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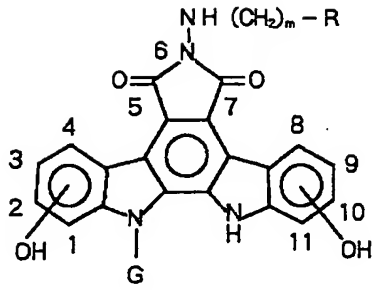
(54) 【Title of Invention】 Antitumor Indolopyrrolocarbazole Derivatives

(57) 【Abstract】
【Problem】 Creation of Novel Antitumor Agents
【Solution Means】
A compound represented by the following general formula or a pharmaceutically acceptable salt thereof
【Com. 1】



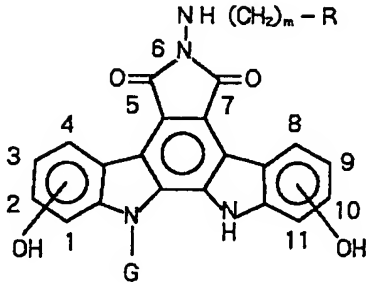
[I]

wherein R represents a phenyl, naphthyl, pyridyl, furyl or thienyl group each of which has one or more substituents selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group except that when the phenyl, naphthyl, pyridyl, furyl or thienyl group has a lower alkoxy group as a substituent, each of which simultaneously has another substituent selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group, m represents an integer of 1 to 3, and G represents a β-D-glucopyranosyl group, and the positions of substitution of the hydroxyl groups on the indolopyrrolocarbazole ring are the 1- and 11-positions, or the 2- and 10-positions.

【Scope of Claims】

【Claim 1】 A compound represented by the general formula or a pharmaceutically acceptable salt thereof

【Com. 1】



[I]

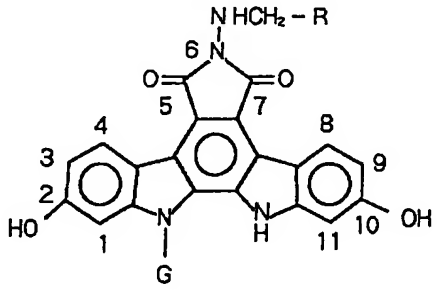
wherein R represents a pheny, naphthyl, pyridyl, furyl or thienyl group each of which has one or more substituents selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group except that when the pheny, naphthyl, pyridyl, furyl or thienyl group has a lower alkoxy group as a substituent, each of which simultaneously has another substituent selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group,

m represents an integer of 1 to 3, and

G represents a β-D-glucopyranosyl group, and the positions of substitution of the hydroxyl groups on the indolopyrrolocarbazole ring are the 1- and 11-positions, or the 2- and 10-positions.

【Claim 2】 The compound represented by the following general formula or the pharmaceutically acceptable salt thereof, according to claim 1

【Com. 2】

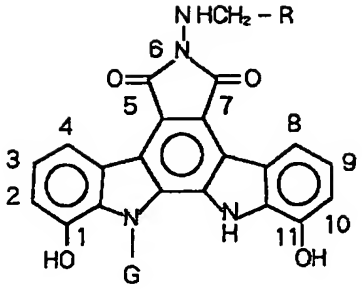


[I－a]

wherein R, m and G are as defined in claim 1.

【Claim 3】 The compound represented by the following general formula or the pharmaceutically acceptable salt thereof, according to claim 1

【Com. 3】



[I − b]

wherein R, m and G are as defined in claim 1.

【Claim 4】 An antitumor agent containing a compound or pharmaceutically acceptable salt thereof according to claim 1,2 or 3.

【Detailed Description of the Invention】

【0001】

【Industrially Applicable Field】

This invention is useful in the pharmaceutical field, and, more detailedly, relates to novel indolopyrrolocarbazole derivatives inhibiting growth of tumor cells and exerting antitumor effect, processes for preparation thereof and their use.

【0002】

【Prior Art】

Many compounds are already put to practical use as pharmaceuticals in the field of tumor chemotherapy. However, their effects are not always sufficient against various kinds of tumors, and the problem of resistance of tumor cells to these drugs also makes the methods of clinical use complicate (see, Proceedings of the 47th Annual Meeting of Japan Cancer Society, pages 12-15, 1988).

【0003】

Under the circumstances, development of novel anticancer substances is always desired in the field of cancer treatment. Particularly, there is need for substances overcoming resistance to existing carcinostatic substances and showing effectiveness against cancers on which existing carcinostatic substances cannot exert sufficient effect.

【0004】

Under these present circumstances, the present inventors have widely screened metabolites of microorganisms, and as a result, they found a novel compound BE-13793C (12,13-dihydro-1,11-dihydroxy-5H-indolo[2.3-a]pyrrolo[3,4-c]carbazole-5,7 (6H) -dione) having antitumor activity (see, EP-A2-0388956).

【0005】

Thereafter, they have tried to create compounds having further excellent antitumor activity by chemically modifying BE-13793C, and disclosed such compounds in prior patent applications (EP-A1-0528030, EP-A1-0545195, WO95/30682 and WO96/04293).

【0006】

【Problems to be Solved by the Invention】

It is a problem to be solved in the present invention to create compounds having further excellent antitumor activity by chemically modifying indolopyrrolocarbazole antitumor substances disclosed in the prior patent applications.

【0007】

【Means for Solving the Problems】

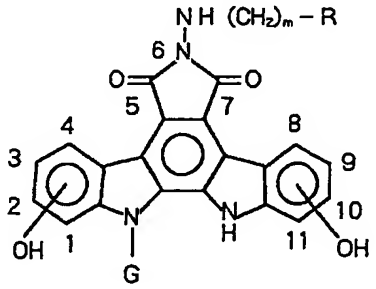
For solving the above problem, the present inventors have synthesized a wide range of indolopyrrolocarbazole derivatives and examined their antitumor activity, and found that compounds represented by the later-described general formula [I] show further excellent antitumor activity than the indolopyrrolocarbazole compounds disclosed in the prior applications, and completed the present invention.

【0008】

Namely, the invention relates to a compound represented by the general formula or a pharmaceutically acceptable salt thereof, and a use thereof:

【0009】

【Com. 4】



[I]

wherein R represents a phenyl, pyridyl, furyl or thienyl group each of which has one or more substituents selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group except that when the phenyl, pyridyl, furyl or thienyl group has a lower alkoxy group as a substituent, each of which simultaneously has another substituent selected from the group consisting of a hydroxyl group, a lower alkoxy group, a hydroxy lower alkyl group and a hydroxy lower alkenyl group, m represents an integer of 1 to 3, and G represents a β-D-glucopyranosyl group, and the positions of substitution of the hydroxyl groups on the indolopyrrolocarbazole ring are the 1- and 11-positions, or the 2- and 10-positions.

【0010】

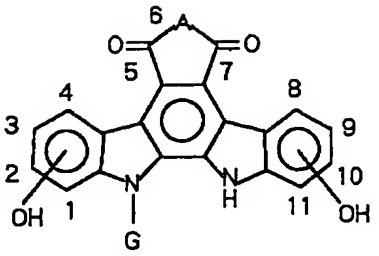
Description is made below on processes for preparing the compounds of the invention.

【0011】

An indolopyrrolocarbazole derivative of the invention can be prepared by reacting a compound represented by the general formula

【0012】

【Com. 5】



[II]

wherein, A represents NH or H, and G is as defined above,
the compound being a known compound disclosed in EP-A1-0528030, EP-A1-0545195, WO95/30682 and WO96/04293, with a compound represented by the general formula

【0013】

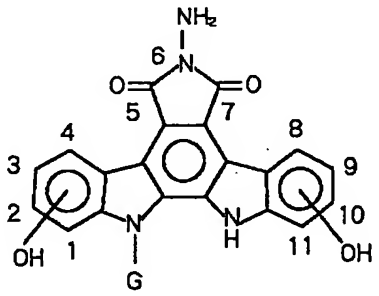
【Com. 6】

$$H_2N\text{-}NH(CH_2)_mR \qquad [III]$$

wherein, R and m are as defined above,
or by condensing a compound represented by the general formula

【0014】

【Com. 7】



[IV]

wherein, G is as defined above,
with a compound represented by the general formula

【0015】

【Com. 8】

$$R^1(CH_2)_mCHO \qquad [V]$$

wherein, R^1 has the same meaning as R or means R wherein hydroxyl groups are protected, and m is as defined above,
then carrying out reduction, and, if necessary, removing the protective groups,
or by reacting a compound of the general formula [IV] with a compound represented by the general formula

【0016】

【Com. 9】

$R^1(CH_2)_mL$ [VI]

wherein, L means a leaving group, and R^1 and m are as defined above,

, and, if necessary, removing the protective groups.

【0017】

The reaction between the compound represented by the general formula [II] and the compound represented by the general formula [III] is reaction between an imide or an acid anhydride and a hydrazine derivative, well-known in the chemical field. This reaction can be carried out using a solvent usually having no bad influenece on the reaction, such as, for example, tetrahydrofuran or N,N-dimethylformamide. The use amount of the compound [III] is usually a little excess to 5 molar equivalents based on the compound [II], but a largely excess use of the former is possible.

【0018】

The reaction temperature is usually in the range of -50℃ to the boiling point of the solvent, but, if necessary, temperature higher than or lower than the temperature can be used. The reaction time is usually in the range of 30 minutes to 2 days, but time longer than or shorter than the time can be used.

【0019】

The reaction of preparing a compound [I] by condensing a compound represented by the general formula [IV] with a compound represented by the general formula [V] and then carrying out reduction can be carried out in the same reaction system, but in some occasion, it is also possible to once isolate the Schiff base as an intermediate product. Namely usually, the reaction can be carried out by mixing the compound [IV] with the compound [V] in a suitable solvent and then adding a reducing agent. The reaction is preferably carried out in the presence of an acid such as acetic acid or hydrochloric acid. As usable solvents, there can, for example, be mentioned alcoholic solvents such as methanol and ethanol, aprotic polar solvents such as N,N-dimethylformamide, etc. The reduction of the Schiff base can be carried out using a metal hydride complex such as sodium cyanoborohydride, or the like, and also by catalytic reduction.

【0020】

The reaction between a compound of the general formula [IV] and a compound of the general formula [VI] is alkylation reaction of an amine, and can be carried out by a known method, for example by reaction with an alkyl halide, alkyl mesylate or alkyl tosylate or the like.

【0021】

The products of the above reactions can be purified by methods known in the field of organic chemistry, for example by precipitation methods, solvent extraction methods, recrystallization, chromatography, etc.

【0022】

Further in the invention, pharmaceutically acceptable salts of compounds obtained by the above processes are included. As such salts, there can be mentioned salts with an alkali metal such as for example potassium or sodium, salts with an alkaline earth metal such as for example calcium, salts with a basic organic compound such as for example ethylamine or arginine, salts with an inorganic acid such as hydrochloric acid or sulfuric acid, and salts with an organic acid such as acetic acid, citric acid or maleic acid.

【0023】

The compounds of the invention represented by the formula [I] show excellent antitumor action.

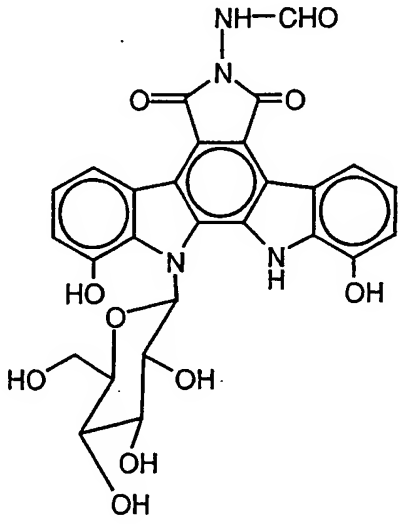
【0024】

Effect on human gastric cancer MX-1

MX-1 solid tumor previously subcutaneously implanted in a nude mouse and grown was thinly cut, and its cubes with each side 3 mm were subcutaneously implanted in test mice. After the implantation, starting from the time when the tumor grew into 0.3 cm^3, various dosages of a test compound were injected once a day for 5 consecutive days into the tail veins of the mice. The same injections were then made for further 5 days after 2 days of interval (treatment schedule: 5/w×2) or once every 3-4 days, four times (treatment schedule: 2/w×2). 20 days or 32 days after the start of the treatment, the length (L) and the breadth (W) of each of the tumors were measured, and its volume (V) was calculated ($V=1/2\times L\times W^2$). A tumor growth inhibition proportion was calculated based on the volume, and a total dose to inhibit tumor growth by 75 % (GID_{75}, mg/kg) was then determined. As a control compound, a compound represented by the following formula was used. The results are shown in Table 1.

【0025】

【Com. 10】



【0026】

【Table 1】

Table 1 Effect of Compounds of the Invention on human gastric cancer MX-1

Test Compound	Treatment Schedule	GID_{75} (mg/kg total)
Example 3	2/w×2	<90
Example 5	5/w×2	<90
Example 10	5/w×2	<90
Example 12	2/w×2	97
Example 14	2/w×2	<12
Example 27	2/w×2	<4.5
Example 28	2/w×2	<36
Example 30	5/w×2	16

Example 31	5/wx2	<30
Example 33	5/wx2	<30
Example 35	5/wx2	82
Example 36	5/wx2	<30
Example 37	5/wx2	32
Example 38	5/wx2	19
Example 39	2/wx2	<30
Control compound	5/wx2	1900

Compounds provided by the present invention show a much better antitumor action than the control compounds, as shown in the above pharmacological test results.

【0027】

As apparent from the results of the above pharmacological tests, the compounds of the invention show an excellent antitumor action, and are useful as antitumor agents for prophylaxis and/or treatment of diseases, especially for treatment of cancers. As administration forms in use as antitumor agents of the compounds of the invention, various forms can be selected, and there can be mentioned peroral agents such as for example tablets, capsules, powders, granules and liquids, or sterilized liquid parenteral agents such as for example solutions and suspensions.

【0028】

Solid preparations such as tablets, capsules, granules and powders can be prepared using compounds of the invention alone, but can also be prepared further using suitable additives. As the suitable additives, there can be mentioned conventional additives, for example, sugars such as for example lactose and glucose, starches such as for example corn, wheat and rice, fatty acids such as for example stearic acid, inorganic salts such as for example magnesium metasilicate aluminate and anhydrous calcium phosphate, synthetic macromolecules such as for example polyvinylpyrrolidone and polyalkylene glycols, fatty acid salts such as for example calcium stearate and magnesium stearate, alcohols such as for example stearyl alcohol and benzyl alcohol, synthetic cellulose derivatives such as for example methylcellulose, carboxymethylcellulose, ethylcellulose and hydroxypropylmethylcellulose, and further, water, gelatin, talc, vegetable oils, gum arabic, etc.

【0029】

These solid preparations such as tablets, capsules, granules and powders can contain, generally 0.1 to 100 % by weight, preferably 5 to 100 % by weight of an effective ingredient.

【0030】

Liquid preparations can be prepared as forms of suspensions, syrups, injections, etc. using suitable additives usually used in liquid preparations, such as water, alcohols or vegetable oils including soybean oil, peanut oil and sesame oil.

【0031】

Particularly, as solvents suitable in parenteral administration including intramuscular injection, intravenous injection and subcutaneous injection, there can for example be mentioned distilled water for injection, aqueous lidocaine hydrochloride solution (for intramuscular injection), physiological saline, aqueous glucose solution, ethanol, polyethylene glycol, liquids for intravenous injection (e.g., aqeous solutions of cetric acid and sodium citrate, etc.), electrolyte solutions (for intravenous injection by drip

and for intravenous injection), etc., or their mixed solutions.

【0032】

These injections may include not only those wherein previous dissolution is made, but also those in the form of dissolving powder alone or with suitable additives when used. These injections usually contain 0.1 to 10 % by weight, preferably 1 to 5 % of an effective ingredient.

【0033】

Liquid preparations such as suspensions and syrups for oral administration can contain 0.5 to 10 % by weight of an effective ingredient.

【0034】

It should be noted that the actually preferred dose of the compounds of the invention is varied depending on kinds of compounds used, kinds of compositions prepared, application frequency, particular sites to be treated, hosts and timors. For example, the dose of each compound per day and per one adult is 10 to 500 mg in the case of oral administration, and 10 to 100 mg in the case of parenteral administration, preferably intravenous injection. The frequency of administration is varied depending on administration methods and symptoms, but the administration can be made in a time or in devided 2 to 5 times. Administration methods including intermittent administration such as every two-days administration or every three-days administration can also be used.

【0035】

【Mode for Carrying out the Invention】

【0036】

【Example】

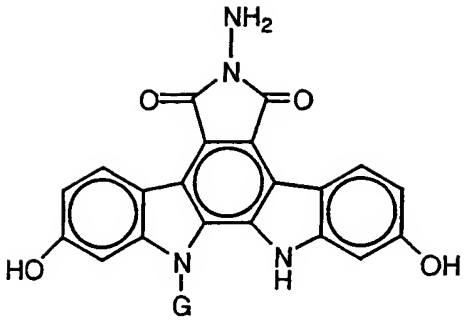
The invention is further specifically described below according to examples, but the invention is not limited to these examples.

【0037】

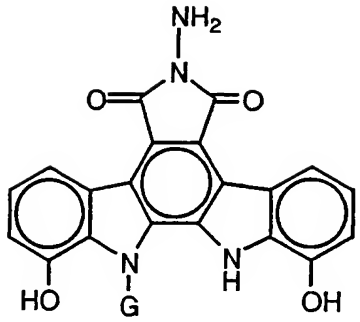
Compounds having the following structural formulae, which were used as starting compounds, are hereinafter referred to as follows.

【0038】

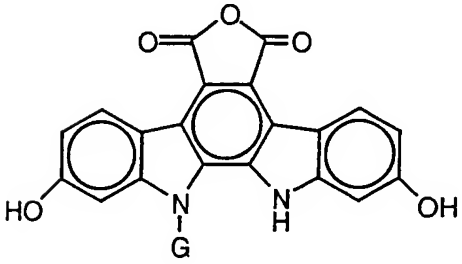
【Com. 11】



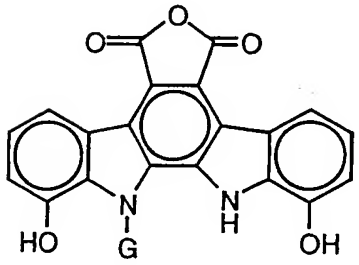
Compound A



Compound B



Compound C



Compound D

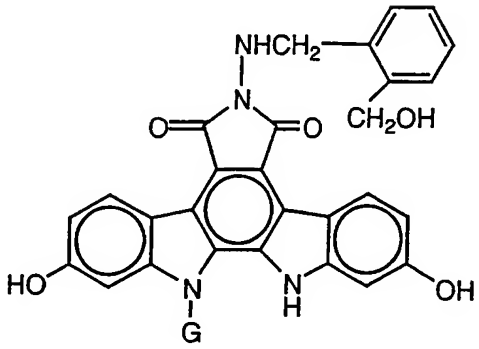
wherein, G represents a β-D-glucopyranosyl group, which is the same in the following examples.

Example 1

Compound represented by the structural formula

【0039】

【Com. 12】



【0040】

25 mg of Compound A and 90 mg of (2-t-butyldimethylsilyloxymethyl)benzyl bromide were dissolved in 1 ml of N,N-dimethylformamide, and the mixture was stirred overnight at room temperature. The resulting reaction mixture was concentrated to dryness, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated, and the concentrate was placed on a Sephadex LH-20 column for

chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was washed with chloroform to obtain 3.6 mg of the compound represented by the above formula.

FAB-MS(m/z):655$(M+H)^+$

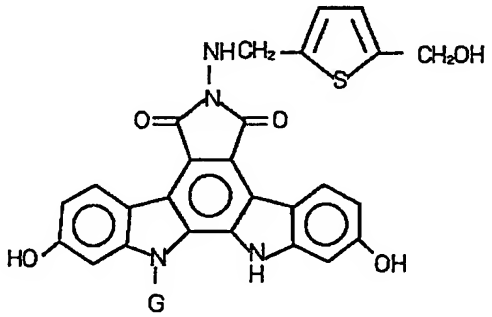
^{1}H-NMR(300MHz,DMSO-d_6,δp pm)11.19(1H,s),9.78(1H,s),9.75(1H,s),8.86(1H,d, J=8.6Hz),8.78(1H,d,J=8.2Hz),7.44(1H,d,J=7.2Hz),7.37(1H,d,J=7.6Hz),7.13-7.28(3H, m),6.98(1H,s),6.78-6.88(2H,m),5.95-6.05(2H,m),5.85(1H,br),5.33(1H,d,J=3.2Hz), 5.10-5.17(2H,m),4.92(1H,d,J=4.0Hz),4.28(2H,d,J=5.2Hz),3.72-4.10(4H,m),3.45-3.55 (2H,m)

Example 2

Compound represented by the structural formula

【0041】

【Com. 13】



30 mg of Compound A and 30 mg of (5-t-butyldimethylsilyloxymethylthiophene)-2-carboxyaldehyde were dissolved in 6 ml of methanol, 30 ml of acetic acid was added, and the mixture was stirred at 80℃ for 4 hours. The reaction mixture was cooled to room temperature, 20 mg of sodium cyanoborohydride and 200 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 27 mg of the compound represented by the above formula.

Rf value: 0.37 (Kieselgel 60F_{254} made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

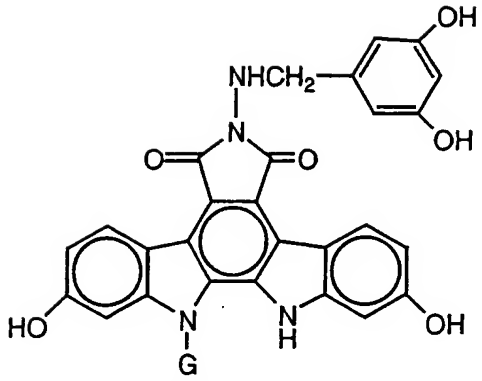
FAB-MS(m/z):660(M^+)

^{1}H-NMR(300MHz,DMSO-d_6 ,δp p m):11.19(1H,s),9.79(1H,s),9.75(1H,s),8.86(1H,d, J=9.3Hz),8.78(1H,d,J=9.0Hz),7.17(1H,d,J=2.1Hz),6.97(1H,d,J=2.1Hz),6.89(1H,d,J=3. 6Hz),6.82(1H,dd,J=2.1,9.3Hz),6.79(1H,dd,J=2.1,9.0Hz),6.73(1H,d,J=3.3Hz),6.10(1H,t ,J=4.5Hz),5.97(1H,d,J=8.1Hz),5.86(1H,t,J=3.3Hz),5.35(1H,t,J=6.0Hz),5.32(1H,d,J=4. 8Hz),5.12(1H,d,J=4.8Hz),4.92(1H,d,J=5.4Hz),4.52(2H,d,J=5.7Hz),4.40(2H,d,J=4.2Hz),4.02(1H,m),3.91(2H,m),3.78(1H,m),3.50(2H,m)

Example 3

Compound represented by the structural formula

【0042】
【Com. 14】



100 mg of Compound A and 131.2 mg of 3,5-dihydroxybenzaldehyde were dissolved in 10 ml of N,N-dimethylformamide, and the mixture was stirred at 80℃ for 48 hours. The reaction mixture was concentrated under reduced pressure, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 90.3 mg of an intermediate compound. 20 mg of this intermediate compound was suspended in 5 ml of methanol, 10 mg of sodium cyanoborohydride and several drops of a 10% solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. After distilling off methanol under reduced pressure, water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated saline, dried and concentrated, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 18 mg of the compound represented by the above formula.

Rf value: 0.30 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

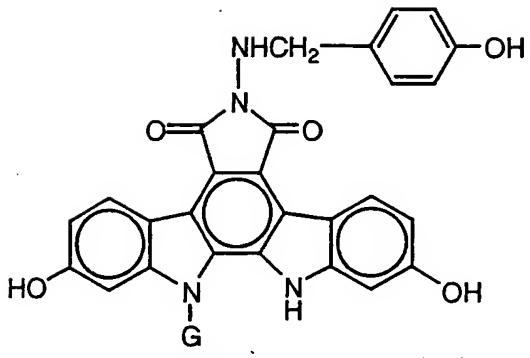
FAB-MS(m/z):657$(M+H)^+$

^{1}H-NMR(300MHz,DMSO-d_6,δp pm)11.19(1H,s),9.77(2H,br),9.11(2H,s),8.87(1H,d, J=8.6Hz),8.79(1H,d,J=8.6Hz),7.17(1H,s),6.97(1H,s),6.78-6.84(2H,m),6.34(2H,s), 6.06(1H,s),5.96(1H,d,J=8.3Hz),5.83-5.87(2H,m),5.34(1H,s),5.12(1H,s), 4.92(1H,d,J=3.9Hz),4.04(2H,d,J=4.5Hz),3.91-3.99(3H,m),3.75-3.88(1H,m),3.49(2H,s)

Example 4

Compound represented by the structural formula

【0043】
【Com. 15】



30 mg of Compound A and 14 mg of 4-hydroxybenzaldehyde were dissolved in 6 ml of methanol, 14 ml of acetic acid was added, and the mixture was stirred at 80℃ for 2 hours. The reaction mixture was cooled to room temperature, 20 mg of sodium cyanoborohydride and 200 ml of a 10% solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 31 mg of the compound represented by the above formula.

Rf value: 0.41 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS(m/z):640(M^+)

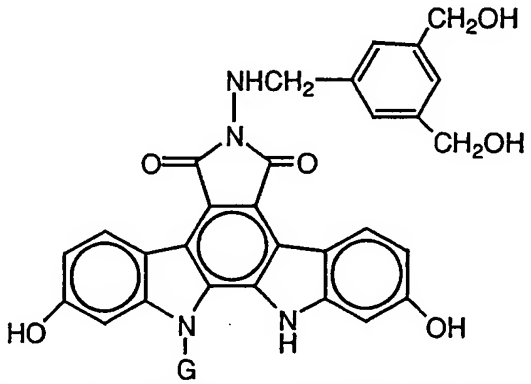
^{1}H-NMR(300MHz,DMSO-d_6,δp pm)11.17(1H,s),9.77(1H,s),9.74(1H,s),9.24(1H,s), 8.86(1H,d,J=8.4Hz),8.78(1H,d,J=8.4Hz),7.25(2H,d,J=8.7Hz),7.17(1H,d,J=1.8Hz),6.97 (1H,d,J=1.8Hz),6.83(1H,dd,J=1.8,8.7Hz),6.80(1H,dd,J=1.8,8.7Hz),6.67(2H,d,J=8.1Hz),5.96(1H,d,J=8.1Hz),5.87(1H,t,J=4.8Hz),5.85(1H,t,J=3.9Hz),5.32(1H,d,J=4.5Hz),5.10 (1H,d,J=5.1Hz),4.91(1H,d,J=4.8Hz),4.12(2H,m),4.03(1H,m),3.91(2H,s),3.78(1H,m),3. 50(2H,m)

Example 5

Compound represented by the structural formula

【0044】

【Com. 16】



30 mg of Compound A and 20 mg of 3,5-dihydroxymethylbenzaldehyde were dissolved in 6 ml of methanol, 20 ml of acetic acid was added, and the mixture was stirred at 80℃ for 3 hours. The reaction mixture was brought back to room temperature, 10 mg of sodium cyanoborohydride and several drops of a 10% solution of hydrochloric acid in methanol were added, and the mixture was stirred at room

temperature for 30 minutes. The reaction mixture was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 22 mg of the compound represented by the above formula.

Rf value: 0.35 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS(m/z):684 (M^+)

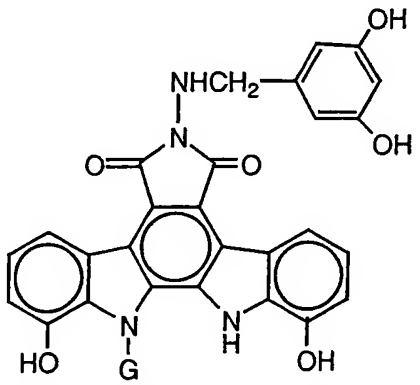
^{1}H-NMR(300MHz,DMSO-d_6,δp pm)11.19(1H,s),9.79(1H,s),9.76(1H,s),8.88(1H,d, J=8.7Hz),8.80(1H,d,J=8.7Hz),7.32(2H,s),7.18(2H,s),6.98(1H,d,J=1.8Hz),6.81(2H,dt,J =1.8,8.7Hz),5.97(1H,d,J=8.7Hz),5.93(1H,t,J=4.8Hz),5.87(1H,t,J=3.2Hz),5.34(1H,d,J= 4.2Hz),5.15(2H,t,J=6.3Hz),5.12(1H,d,J=4.8Hz),4.92(1H,d,J=4.8Hz),4.49(2H,s),4.47(2 H,s),4.22(2H,d,J=5.1Hz),4.03(1H,m),3.92(2H,s),3.78(1H,m),3.50(2H,m)

Example 6

Compound represented by the structural formula

【0045】

【Com. 17】



53 mg of Compound B and 69 mg of 3,5-dihydroxybenzaldehyde were dissolved in 3 ml of N,N-dimethylformamide, and the mixture was stirred overnight at 80℃. The reaction mixture was concentrated under reduced pressure, the concentrate was dissolved in 10 ml of methanol, an excess amount of sodium cyanoborohydride and 0.5 ml of a 10% solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, water was added, the mixture was extracted with a mixed solvent of ethyl acetate/methyl ethyl ketone, and the organic layer was washed with saturated saline, dried and concentrated. The residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 4.8 mg of the compound represented by the above formula.

Rf value: 0.2 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; chloroform:methanol=3:1)

FAB-MS(m/z):657$(M+H)^+$

^{1}H-NMR(300MHz,DMSO-d_6,δp pm)10.89(1H,s),10.33(1H,br),9.97(1H,br),9.11(1H, s),8.70(1H,d,J=6.8Hz),8.52(1H,d,J=7.7Hz),7.15-7.21(2H,m),6.98-7.06(3H,m),6.36(2H, d,J=1.9Hz),6.06(1H,s),5.91(1H,t,J=5.4Hz),5.41(1H,d,J=5.6Hz),5.30-5.45(1H,m),

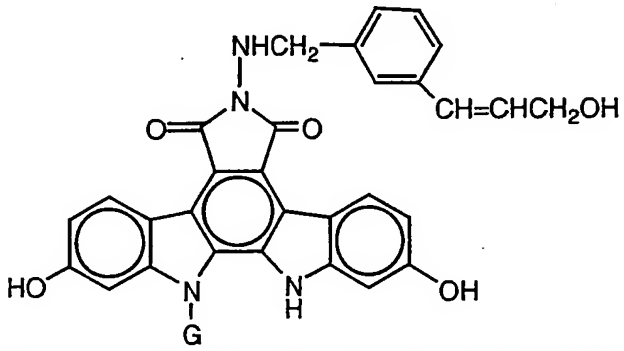
5.20(1H,d,J=4.6Hz),4.87(1H,m),3.94-4.10(4H,m),3.56-3.77(3H,m),3.38-3.43(2H,m)

Example 7

Compound represented by the structural formula

【0046】

【Com. 18】



30 mg of Compound C and 30 mg of 3-(3-hydroxypropenyl)benzylhyrazine trifluoroacetate salt were dissolved in 2 ml of N,N-dimethylformamide, several drops of triethylamine was added, and the mixture was stirred overnight at 80℃. The reaction mixture was concentrated to dryness, and the residue was purified by preparative thin layer chromatography (developing solvent ; acetonitrile: tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1) to obtain 8.2 mg of the compound represented by the above formula.

Rf value: 0.51 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS(m/z):

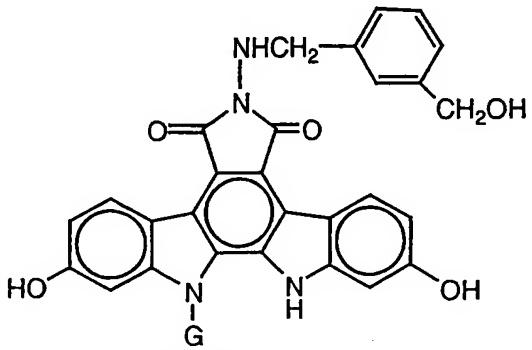
^{1}H-NMR (300MHz,DMSO-d_6,δp pm)11.18(1H,s),9.50-10.00(2H,br),8.86(1H,d, J=8.1Hz),8.78(1H,d,J=8.5Hz),7.59(1H,s),7.20-7.40(3H,m),7.16(1H,s),6.97(1H,s),6.73-6.89(2H,m),6.42(1H,d,J=3.6Hz),6.31-6.48(1H,m),6.10(1H,t,J=4.0Hz),5.95(1H,d, J=7.9Hz),5.88(1H,br),5.36(1H,br),5.13(1H,br),4.91(1H,br),4.84(1H,br),4.26(2H,s),4.09(2H,s),3.70-4.10(4H,m),3.41-3.58(2H,m)

Example 8

Compound represented by the structural formula

【0047】

【Com. 19】



45.5 mg of Compound C and 67.2 mg of 3-hydroxymethylbenzylhyrazine trifluoroacetate salt were dissolved in 3 ml of N,N-dimethylformamide, several drops

of aqueous saturated sodium bicarbonate solution was added, and the mixture was stirred overnight at 70℃. The reaction mixture was diluted with methyl ethyl ketone, washed successively with dilute hydrochloric acid, water and saturated saline,. dried and concentrated. The residue was roughly purified by preparative thin layer chromatography (developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1), placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 1.6 mg of the compound represented by the above formula.

Rf value: 0.40(Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS(m/z): 654 (M^+)

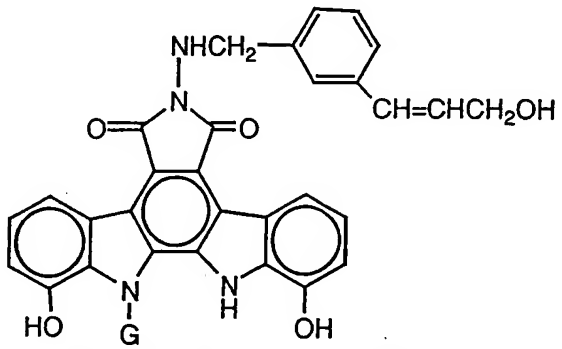
^{1}H-NMR(300MHz,DMSO-d_6,δp pm)11.18(1H,s),8.86(1H,d,J=8.4Hz),8.78(1H,d, J=8.7Hz),7.42(1H,s),7.40(1H,d,J=7.5Hz),7.27(1H,t,J=7.2Hz),7.18(1H,d,J=7.5Hz),7.17 (1H,s),6.98(1H,d,J=1.8Hz),6.81(2H,dt,J=1.8,8.1Hz),6.00(2H,dt,J=1.5,4.8Hz),5.95(1H, d,J=8.7Hz),5.43(1H,br),5.16(2H,br),4.93(1H,br),4.47(2H,s),4.25(1H,d,J=4.8Hz),4.10(1H,br),4.02(1H,d,J=10.8Hz),3.90(2H,m),3.76(1H,m)

Example 9

Compound represented by the structural formula

【0048】

【Com. 20】



30 mg of Compound D and 40 mg of 3-(3-hydroxypropenyl)benzylhyrazine trifluoroacetate salt were dissolved in 1 ml of N,N-dimethylformamide, 0.5 ml of triethylamine was added, and the mixture was stirred at 80℃ for 1.5 hours. The reaction mixture was diluted with a mixed solvent of ethyl acetate/methyl ethyl ketone, washed successively with dilute hydrochloric acid and saturated saline, dried and concentrated. The residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated, and the concentrate was placed again on a Sephadex LH-20 column for chromatography and eluted with ethanol. Fractions containing the desired compound were concentrated to dryness to obtain 7.8 mg of the compound represented by the above formula.

Rf value: 0.48 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

^{1}H-NMR(300MHz,DMSO-d_6,δp pm)10.89(1H,s),10.35(1H,br),9.95(1H,br),8.70(1H, d,J=7.8Hz),8.52(1H,d,J=7.8Hz),7.60(1H,s),6.91-7.40(8H,m),6.53(1H,d,J=16.2Hz), 6.39(1H,td,J=4.6,16.2Hz),6.16(1H,t,J=5.6Hz),5.41(1H,d,J=5.6Hz),5.35(1H,br),5.20(1

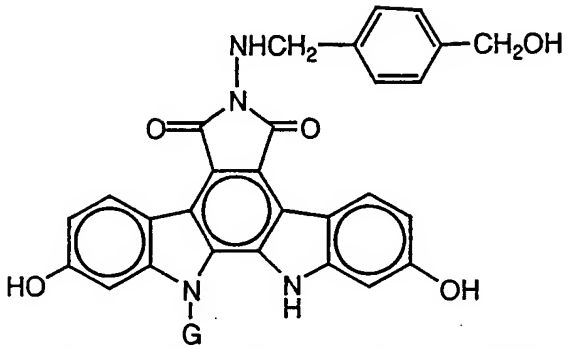
H,d,J=4.9Hz),4.86(1H,t,J=3.6Hz),4.84(1H,t,J=5.6Hz),4.28(2H,s),3.89-4.12(4H,m), 3.30-3.78(4H,m)

Example 10

Compound represented by the structural formula

【0049】

【Com. 21】



100 mg of Compound C and 100 mg of 4-hydroxymethylbenzylhyrazine hydrochloride were dissolved in 5 ml of N,N-dimethylformamide, 0.5 ml of aqueous saturated sodium bicarbonate solution was added, and the mixture was stirred at room temperature for 1 hour and then at 80℃ for 30 minutes. The reaction mixture was diluted with methyl ethyl ketone, washed successively with 2N hydrochloric acid and saturated saline, dried and concentrated. The residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 33 mg of the compound represented by the above formula.

Rf value: 0.47 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; chloroform:methanol:tetrahydrofuran=2:1:1)

FAB-MS (m/z): 655 $(M+H)^+$

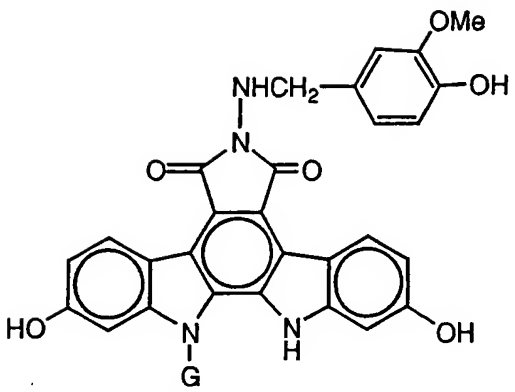
^{1}H-NMR (300MHz,DMSO-d_6,δppm)11.10(1H,br),8.83(1H,d,J=9.3Hz),8.73(1H,d, J=8.4Hz),7.44(2H,d,J=8.4Hz),7.23(2H,d,J=7.8Hz),7.11(1H,s),6.94(1H,s),6.78(2H,dt,J =9.0,2.1Hz),6.02(1H,t,J=4.8Hz),5.92(1H,d,J=8.1Hz),4.80-5.23(2H,br),4.43(2H,s), 4.24(2H,s),4.03(1H,m),3.90(2H,m),3.77(1H,m),3.50(2H,m),3.25-3.42(3H,m)

Example 11

Compound represented by the structural formula

【0050】

【Com. 22】



52 mg of Compound C and 61.4 mg of 3-methoxy-4-hydroxybenzylhyrazine hydrochloride were dissolved in 2 ml of N,N-dimethylformamide, 0.5 ml of aqueous saturated sodium bicarbonate solution was added, and the mixture was stirred at 80℃ for 1 hour. The reaction mixture was concentrated to dryness, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 20 mg of the compound represented by the above formula.

Rf value: 0.33 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; chloroform:methanol:tetrahydrofuran=3:1:1)

FAB-MS (m/z): 655 $(M+H)^+$

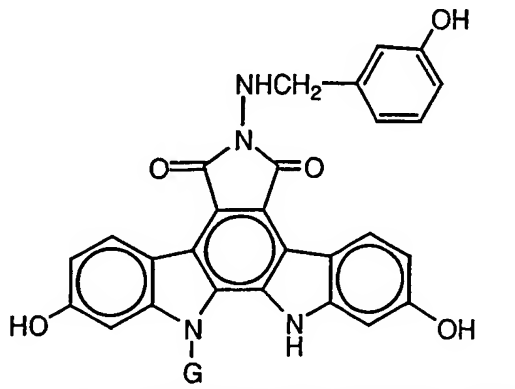
^{1}H-NMR (300MHz,DMSO-d_6,δppm)11.12(1H,s),9.77(1H,s),8.74(1H,s),8.86(1H,s), 8.78(1H,d,J=8.6Hz),8.76(1H,s),7.16(2H,d,J=8.1Hz),6.97(1H,s),6.70-6.85(3H,m),6.64 (1H,d,J=8.5Hz),5.86-6.04(2H,m),5.85(1H,t,J=3.6Hz),5.32(1H,d,J=3.9Hz),5.10(1H,d, J=4.2Hz),4.90(1H,d,J=4.3Hz),4.11-4.21(2H,m),3.86-4.10(4H,m),3.77(3H,m),3.35-3.52(2H,m)

Example 12

Compound represented by the structural formula

【0051】

【Com.23】



40 mg of Compound C and 31 mg of 3-hydroxybenzylhyrazine hydrochloride were dissolved in 2 ml of N,N-dimethylformamide, 0.5 ml of aqueous saturated sodium bicarbonate solution was added, and the mixture was stirred overnight at 80℃. The reaction mixture was diluted with ethyl acetate, washed successively with 2N hydrochloric acid, aqueous saturated sodium bicarbonate solution and saturated saline, dried and concentrated. The residue was placed on a Sephadex LH-20 column for

chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 17.2 mg of the compound represented by the above formula.

Rf value: 0.24 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS (m/z): 641 $(M+H)^+$

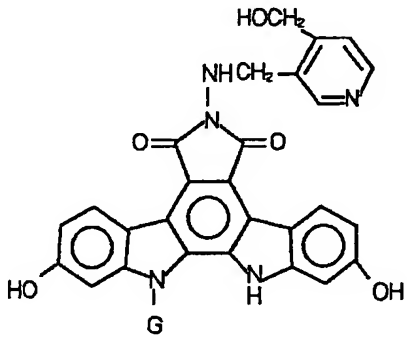
^{1}H-NMR (300MHz,DMSO-d_6,δp pm)11.18(1H,s),9.76(1H,s),9.73(1H,s),9.28(1H,s), 8.87(1H,d,J=8.5Hz),8.79(1H,d,J=9.0Hz),7.17(1H,s),7.18(1H,dd,J=7.5,8.0Hz),6.97(1H, d,J=2.3Hz),6.78-6.93(4H,m),6.60(1H,dd,J=1.5,8.0Hz),5.96(2H,m),5.85(1H,m),5.30 (1H,d,J=4.2Hz),5.09(1H,d,J=4.9Hz),4.90(1H,d,J=5.1Hz),4.15(2H,s),3.72-4.05(4H,m) 3.50(2H,m)

Example 13

Compound represented by the structural formula

【0052】

【Com. 24】



43 mg of Compound A and 100 mg of (3-t-butyldimethylsilyloxymethyl)-3-pyridinecarbaldehyde were suspended in 10 ml of methanol, 18 ml of acetic acid was added, and the mixture was stirred overnight at 80℃. The reaction mixture was concentrated, put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was dissolved in 5 ml of a mixed solvent of methanol/tetrahydrofuran (1:1). 5 % palladium-carbon was added and the mixture was stirred at room temperature for 3.5 hours under a hydrogen stream. The reaction mixture was filtered using Celite and the residue was dissolved in 5 ml of tetrahydrofuran. An excess amount of tetrabutylammonium fluoride (1.0 M tetrahydrofuran solution) was added and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated, put on a Sephadex LH-20 column for chromatography, and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 4.3 mg of the compound represented by the above formula.

Rf value: 0.1 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):656$(M+H)^+$

^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):11.18(1H,s),9.75(1H,s),9.73(1H,s),8.84(1H,d,

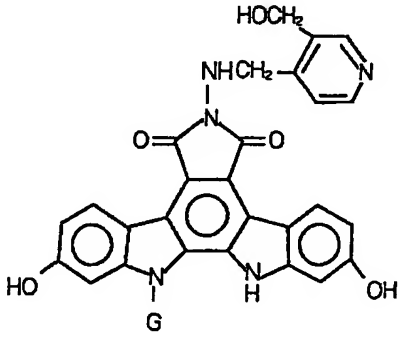
J=8.4Hz),8.77(1H,d,J=8.9Hz),8.42(1H,d,J=4.9Hz),8.39(1H,s),7.48(1H,d,J=4.9Hz),7.17(1H,d,J=1.1Hz),6.97(1H,s),6.78-6.83(2H,m),609(1H,t,J=4.7Hz),5.97(1H,d,J=6.6Hz),5.84(1H,t,J=3.8Hz),5.39(1H,t,J=5.8Hz),5.30(1H,d,J=4.8Hz),5.09(1H,d,J=4.2Hz),4.95(2H,d,J=5.3Hz),4.90(1H,d,J=3.3Hz),4.27(2H,d,J=4.2Hz),3.75-4.03(4H,m),3.47-3.52 (2H,m)

Example 14

Compound represented by the structural formula

【0053】

【Com. 25】



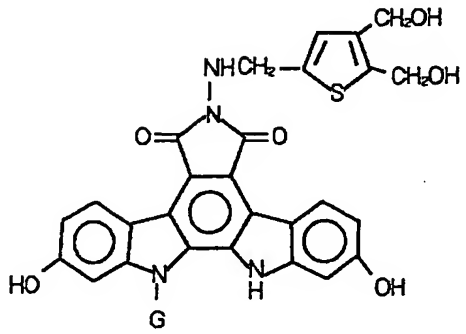
98 mg of Compound A and 92.1 mg of 4-(3-t-butoxymethyl)pyridinecarbaldehyde were dissolved in 5 ml of methanol, 18 ml of acetic acid was added, and the mixture was stirred overnight at 80℃. The reaction mixture was concentrated, and the resulting crystals were washed with chloroform and dissolved in a mixed solvent of methanol/tetrahydrofuran (1:1). 5 % palladium-carbon was added and the mixture was stirred for 3 hours under a hydrogen stream. The reaction mixture was filtered using Celite and the filtrate was concentrated. The residue was dissolved in tetrahydrofuran, tetrabutylammonium fluoride was added, and the mixture was stirred at room temperature for 30 minutes. Water was added, the mixture was extracted with methyl ethyl ketone, and the organic layer was washed with an aqueous saturated sodium chloride solution and concentrated. The concentrate was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 13.5 mg of the compound represented by the above formula.

Rf value: 0.10 (Kieselgel 60F_{254} made by Merck Co., developing solvent; chloroform: methanol: tetrahydrofuran = 2:2:1)

FAB-MS(m/z):656$(M+H)^+$

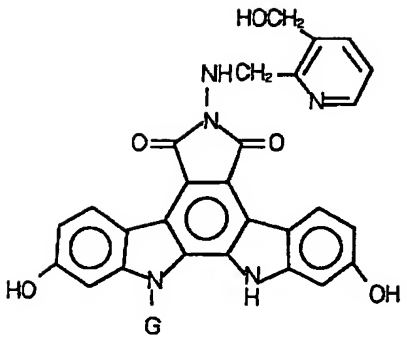
^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):11.19(1H,s),9.78(1H,s),9.75(1H,s)8.85(1H,d,J=9.1Hz),8.77(1H,d,J=9.1Hz),8.51(1H,s),8.11(1H,d,J=5.1Hz),7.59(1H,d,J=4.6Hz),7.17(1H,d,J=2.1Hz),6.97(1H,d,J=1.8Hz),6.79-6.85(2H,m),6.25(1H,t,J=5.0Hz),5.98(1H,d,J=8.3Hz),5.86(1H,d,J=4.5Hz),5.32(1H,d,J=4.5Hz),5.23(1H,t,J=5.6Hz),5.11(1H,d,J=4.4Hz),4.91(1H,d,J=4.9Hz),4.74(2H,d,J=5.2Hz),4.35(2H,d,J=7.8Hz),3.73-4.05(4H,m),3.43-3.52(2H,m)

Example 15
Compound represented by the structural formula
【0054】
【Com. 26】



50 mg of Compound A and 100 mg of (4,5-t-butyldimethylsilyloxymethyl) thiophene-2-carboxyaldehyde were suspended in 10 ml of anhydrous methanol, 100 ml of acetic acid was added, and the mixture was stirred at 80℃ for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 40 mg of an intermediate compound. This was suspended in 3 ml of methanol, 12 mg of sodium cyanoborohydride and and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was purified by preparative thin layer chromatography (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1) to obtain 26 mg of the compound represented by the above formula.
Rf value: 0.28 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)
FAB-MS(m/z):690(M^+)
^{1}H-NMR(300MHz,DMSO-d_6,δppm):11.17(1H,s),9.50-10.15(2H,br),8.86(1H,d, J=8.4Hz),8.78(1H,d,J=8.7Hz),7.16(1H,d,J=1.8Hz),6.97(1H,d,J=2.1Hz),6.92(1H,s),6.82(1H,dd,J=1.8,8.7Hz),6.79(1H,dd,J=2.1,8.4Hz),6.04(1H,t,J=5.1Hz),6.04(1H,t.J=5.1Hz),5.96(1H,d,J=8.1Hz),5.88(1H,br),5.35(1H,br),5.28(1H,br),5.15(1H,br),4.93(2H,br),4.53(2H,br),4.73(2H,d,J=4.5Hz),4.30(1H,s),4.00(1H,m),3.91(2H,m),3.77(1H,m),3.52(2H,m)

Example 16
Compound represented by the structural formula
【0055】
【Com. 27】



30 mg of Compound A and 50 mg of 2-(3-t-butyldimethylsilyloxymethyl) pyridinecarbaldehyde were suspended in 6 ml of methanol, 30 ml of acetic acid was added, and the mixture was stirred at 80℃ for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to obtain 40 mg of an intermediate compound. This was dissolved in a mixed solvent of tetrahydrofuran/methanol (2:1), 15 mg of sodium cyanoborohydride and 3 ml of a solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 3 hour. The reaction mixture was concentrated, put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 27 mg of the compound represented by the above formula.

Rf value: 0.12 (Kieselgel 60F_{254} made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):656$(M+H)^+$

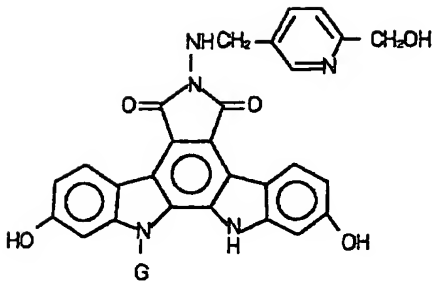
^{1}H-NMR(300MHz,DMSO-d_6 ,δppm):11.18(1H,br),9,77(2H,br,)8,82(1H,d, J=9.0Hz), 8.784(1H,d,J=9.0Hz),8.27(1H,dd,J=1.8,5.1Hz),7.83(1H,d,J=8.1Hz),7.28(1H,dd,J=8.1, 5.1Hz),7.17(1H,d,J=1.8Hz),6.98(1H,d,J=1.8Hz),6.82(1H,dd,J=1.8,9.1Hz),6.79(1H,dd, J=1.8,9.0Hz),6.15(1H,t,J=5.1Hz),5.97(1H,d,J=8.1Hz),5.86(1H,t,J=4.2Hz),5.33(1H,d,J =5.4Hz),5.31(1H,d,J=5.4Hz),5.12(1H,d,J=4.8Hz),4.93(1H,d,J=4.5Hz),4.87(2H,d,J=6.0 Hz),4.36(2H,d,J=5.1Hz),4.03(1H,m),3.91(2H,s),3.79(1H,m),3.51(2H,m)

Example 17

Compound represented by the structural formula

【0056】

【Com. 28】



30 mg of Compound C and 65 mg of (6-hydroxymethyl-3-pyridylmethyl)hydrazine hydrochloride were dissolved in 5 ml of N,N-dimethylformamide, 0.5 ml of triethylamine was added, and the mixture was stirred at 80℃ for 3 hours. 33 mg of (6-hydroxymethyl-3-pyridylmethyl)hydrazine hydrochloride was added and the mixture was stirred at 80℃ for 2 hours. The reaction mixture was concentrated to dryness, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated, and the residue was again put on a Sephadex LH-20 column for chromatography and eluted with ethanol. Fractions containing the desired compound were concentrated to dryness to obtain 7.2 mg of the compound represented by the above formula.

FAB-MS(m/z):656$(M+H)^+$

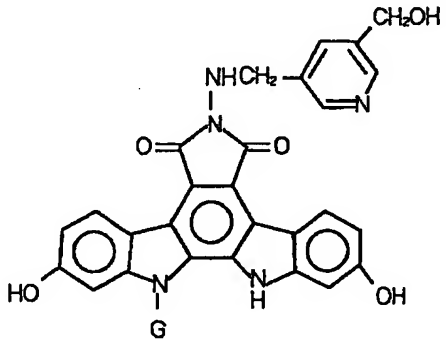
^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):11.12(1H,br),8.81(1H,d,J=8.7Hz),8.73(1H, d,J=8.7Hz),8.51(1H,s),7.90(1H,d,J=7.9Hz),7.39(1H,d,J=7.9Hz),7.11(1H,s),6.93(1H,s), 6.77(2H,t,J=8.7Hz),6.21(1H,t,J=3.8Hz),5.92(1H,d,J=7.9Hz),4.85-5.50(5H,br),4.48(2H, s),4.27(2H,d,J=3.8Hz),3.70-4.05(4H,m),3.45-3.52(2H,m)

Example 18

Compound represented by the structural formula

【0057】

【Com. 29】



12.5 mg of Compound C and 42 mg of (5-hydroxymethyl-3-pyridylmethyl) hydrazine hydrochloride were dissolved in 1 ml of N,N-dimethylformamide, 0.1 ml of triethylamine was added, and the mixture was stirred at 80℃ for 2.5 hours. 0.1 ml of triethylamine was added and the mixture was stirred overnight at 50℃. The reaction mixture was concentrated to dryness, and the residue was put on a Sephadex LH-20

column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated, and the residue was again put on a Sephadex LH-20 column for chromatography and eluted with ethanol. Fractions containing the desired compound were concentrated to dryness to obtain 2.4 mg of the compound represented by the above formula.

Rf value: 0.18 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):656$(M+H)^+$

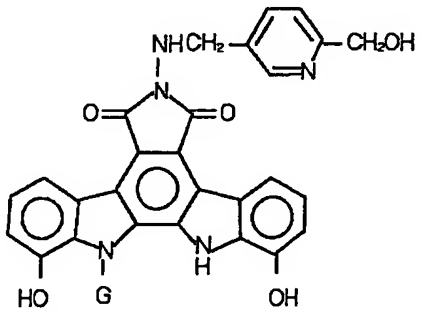
^{1}H-NMR(300MHz,DMSO-d_6,δppm):11.18(1H,br),9.60-10.02(2H,br),8.84(1H,d, J=8.5Hz),8.76(1H,d,J=8.6Hz),8.55(1H,s),8.37(1H,s),7.84(1H,s),7.16(1H,s),7.00(1H,s), 6.75-6.85(2H,m),6.21(1H,t,J=4.7Hz),5.95(1H,d,J=7.8Hz),5.88-5.95(1H,br),5.40-5.48 (1H,br),5.26-5.35(1H,br),5.15-5.25(1H,br),4.90-4.93(1H,br),4.56(2H,d,J=4.7Hz),4.50 (2H, s),3.72-4.05(4H,m),3.45-3.55(2H,m)

Example 19

Compound represented by the structural formula

【0058】

【Com. 30】



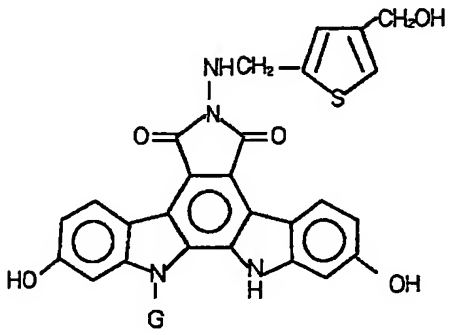
30 mg of Compound D and 65 mg of (6-hydroxymethyl-3-pyridylmethyl)hydrazine hydrochloride were dissolved in 5 ml of N,N-dimethylformamide, 0.5 ml of triethylamine was added, and the mixture was stirred at 80℃ for 1.5 hours. The reaction mixture was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 29 mg of the compound represented by the above formula.

FAB-MS(m/z):656$(M+H)^+$

^{1}H-NMR(300MHz,DMSO-d_6,δppm):10.89(1H,br),10.36(1H,br),9.97(1H,br),8.67 (1H,d,J=7.9Hz),8.52(1H,d,J=2.2Hz),8.50(1H,d,J=7.9Hz),7.93(1H,dd,J=2.2,8.1Hz),7.4 1(1H,d,J=8.1Hz),7.18(2H,t,J=7.9Hz),7.02(1H,d,J=7.9Hz),7.00(2H,t,J=7.9Hz),6.29(1H, t,J=4.5Hz),5.42(1H,d,J=5.6Hz),5.33(1H,d,J=6.1Hz),5.32(1H,t,J=6.0Hz),5.21(1H,d,J=5 .3Hz),4.82-4.91(1H,br),4.48(2H,d,J=6.0Hz),4.29(2H,d,J=4.5Hz),3.91-4.12(2H,m), 3.52-3.79(3H,m),3.30-3.40(1H,m)

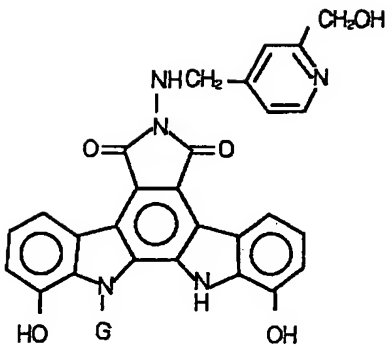
Example 20

Compound represented by the structural formula
【0059】
【Com. 31】



30 mg of Compound B and 152 mg of 4-(t-butyldimethylsilyloxyethyl)thiophene-2-carbaldehyde were suspended in 6 ml of anhydrous methanol, 30 ml of acetic acid was added, and the mixture was stirred at 80℃ for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 31 mg of an intermediate compound. This was suspended in 3 ml of methanol, 30 mg of sodium cyanoborohydride and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, dried and concentrated. The residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 5 mg of the compound represented by the above formula.
Rf value: 0.43 (made by Merck Co., toluene: water: acetic acid = 4:2:2:0.5:0.1)
FAB-MS(m/z):675$(M)^+$
^{1}H-NMR(300MHz,DMSO-d_6 ,δppm):11.19(1H,s),9.80(2H,br),8.86(1H,d,J=9.0Hz),8.78(1H,d,J=8.7Hz),7.17(1H,d,J=1.8Hz),7.03(1H,s),6.98(1H,d,J=2.1Hz),6.95(1H,s),6.80(2H,dt,J=2.1,8.7Hz),6.08(1H,t,J=5.1Hz),5.96(1H,d,J=7.8Hz),5.89(1H,br),5.36(1H,br),5.13(1H,br),4.93(1H,br),4.57(1H,br),4.38(2H,d,J=4.2Hz),4.05(2H,m),3.92(2H,s),3.77(1H,m),3.50(5H,m)

Example 21
Compound represented by the structural formula
【0060】
【Com. 32】



17 mg of Compound D and 12 mg of 4-(2-hydroxymethyl-4-pyridylmethyl) hydrazine trifluoroacetate were dissolved in 2 ml of N,N-dimethylformamide, 0.1 ml of triethylamine was added, and the mixture was stirred at 75℃ for 2 hours. Water and ethyl acetate were added to the reaction mixture, and the mixture was extracted three times with water. Sodium chloride was added to the aqueous layer and the mixture was extracted three times with methyl ethyl ketone. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 8 mg of the compound represented by the above formula.

FAB-MS(m/z):656$(M+H)^+$

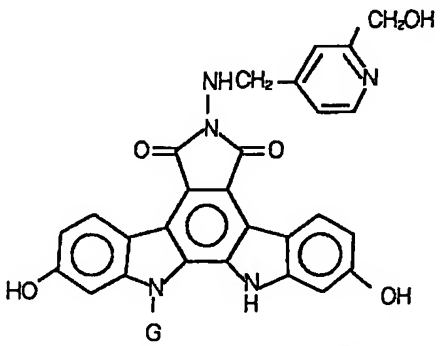
^{1}H-NMR(300MHz,DMSO-d_6,δppm):10.90(1H,br),8.66(1H,d,J=7.6Hz),8.50(1H,d, J=7.6Hz),8.41(1H,d,J=5.0Hz),7.57(1H,s),7.48(1H,d,J=5.0Hz),7.17(2H,t,J=7.6Hz),7.07 (1H,d,J=7.6Hz),7.00(1H,d,J=7.6Hz),6.98(1H,t,J=7.6Hz),6.32(1H,t,J=4.8Hz),5.36(1H,t, J=3.7Hz),5.10-5.50(4H,br),4.51(2H,d,J=3.7Hz),4.34(2H,d,J=4.8Hz),3.91-4.12(2H,m), 3.51-3.80(3H,m)

Example 22

Compound represented by the structural formula

【0061】

【Com. 33】



17 mg of Compound C and 12 mg of (2-hydroxymethyl-4-pyridylmethyl)hydrazine

trifluoroacetate were dissolved in 1 ml of N,N-dimethylformamide, 0.1 ml of triethylamine was added, and the mixture was stirred at 80℃ for 3.5 hours. Water and ethyl acetate were added to the reaction mixture, and the mixture was separated into two layers. Sodium chloride was added to the aqueous layer and the mixture was extracted with methyl ethyl ketone. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 4 mg of the compound represented by the above formula.

FAB-MS(m/z):656($M+H^+$)

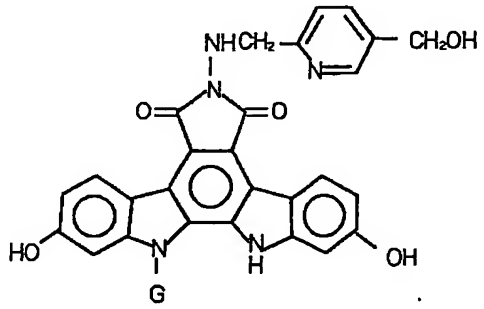
^{1}H-NMR(300MHz,DMSO-d_6,δppm):11.17(1H,br),9.55-10.05(2H,br),8.85(1H,d, J=8.4Hz),8.77(1H,d,J=8.2Hz),8.41(1H,d,J=5.1Hz),7.56(1H,s),7.47(1H,d,J=5.1Hz),7.15(1H,s),6.96(1H,s),6.72-6.85(2H,m),6.26(1H,t,J=4.9Hz),5.94(1H,d,J=8.6Hz),5.80-5.99(1H,br),5.30-5.42(2H,br),5.10-5.20(1H,br),4.85-4.95(1H,br),4.51(2H,d,J=1.8Hz),4.32(2H,d,J=4.5Hz),3.89-4.04(1H,m),3.90(2H,m),3.74-3.78(1H,m),3.50 (2H,m)

Example 23

Compound represented by the structural formula

【0062】

【Com. 34】



14 mg of Compound A and 14.7 mg of 5-t-butyldimethylsilyloxymethylpyridine-2-carbaldehyde were suspended in 2 ml of anhydrous methanol, 8 ml of acetic acid was added, and the mixture was stirred overnight at 80℃. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 15.3 mg of an intermediate compound. 75 mg of sodium cyanoborohydride was suspended in 1 ml of tetrahydrofuran, and 0.55 ml of zinc chloride (1.0 M diethyl ether solution) was added dropwise. A suspension of 15.3 mg of the intermediate compound in 3 ml of tetrahydrofuran was added, and the mixture was stirred at room temperature for 2.5 hours. An aqueous saturated sodium bicarbonate solution was added to the reaction mixture, and the mixture was extracted with methyl ethyl ketone. The organic layer was dried and concentrated, the residue was dissolved in 3 ml of tetrahydrofuran, and an excess amount of tetrabutylammonium fluoride (1 M tetrahydrofuran solution) was added dropwise at 0℃. The mixture was stirred at room temperature for 30 minutes, water was added, and the mixture was extracted with methyl ethyl ketone. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20

column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 4.5 mg of the compound represented by the above formula.

Rf value: 0.1 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; chloroform: methanol: tetrahydrofuran = 3:1:1)

FAB-MS(m/z):656$(M+H)^+$

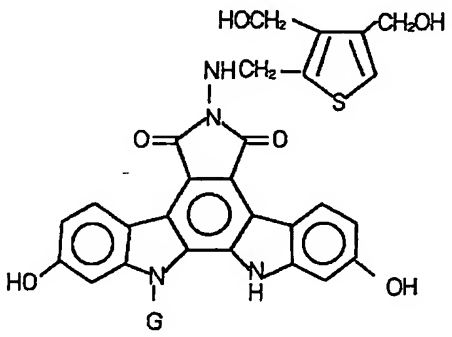
^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):11.18(1H,s),9.77(2H,br),8.84(1H,d,J=8.5Hz), 8.76(1H,d,J=8.6Hz),8.35(1H,d,J=1.7Hz),7.72(2H,s),7.17(1H,d,J=1.7Hz),6.98(1H,d,J= 1.9Hz),6.78-6.98(2H,m),6.22(1H,t,J=4.6Hz),5.96(1H,d,J=8.9Hz),5.87(1H,br),5.35(1H, br),5.22(1H,t,J=2.0Hz),5.11(1H,br),4.91(1H,br),4.46(2H,d,J=4.2Hz),4.35(2H,d,J=4.6H z),3.73-4.09(4H,m),3.49(2H, s)

Example 24

Compound represented by the structural formula

【0063】

【Com. 35】



30 mg of Compound A and 30 mg of 3,4-bis-(t-butyldimethylsilyloxymethyl) thiophene-2-carbaldehyde were suspended in 6 ml of anhydrous methanol, 30 ml of acetic acid was added, and the mixture was stirred at 80℃ for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 31 mg of an intermediate compound. This was suspended in 5 ml of methanol, 10 mg of sodium cyanoborohydride and 100 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, and washed with water and an aqueous saturated sodium chloride solution. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 25 mg of the compound represented by the above formula.

Rf value: 0.30 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):691$(M+H)^+$

^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):11.19(1H,s),9.79(1H,s),9.76(1H,s),8.86(1H,

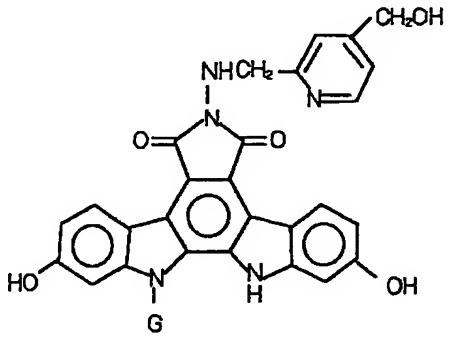
d,J=8.4Hz),8.78(1H,d,J=8.7Hz),7.18(1H,d,J=1.8Hz),7.15(1H,s),6.98(1H,d,J=2.1Hz),6.82(2H,dt,J=8.7,1.8Hz),6.04(1H,t,J=5.4Hz),5.97(1H,d,J=8.1Hz),5.86(1H,t,J=3.6Hz),5.33(1H,d,J=4.2Hz),5.12(1H,d,J=4.2Hz),5.01(1H,t,J=6.0Hz),4.93(1H,d,J=4.8Hz),4.85(1H,t,J=5.7Hz),4.52(2H,d,J=5.7Hz),4.70(2H,d,J=5.7Hz),4.40(2H,d,J=4.8Hz),4.01(1H,m),3.92(2H,m),3.77(1H,m),3.50(2H,m)

Example 25

Compound represented by the structural formula

【0064】

【Com. 36】



18 mg of Compound A and 7 mg of 4-hydroxymethylpyridine-2-carbaldehyde were suspended in 2 ml of anhydrous methanol, several drops of acetic acid were added, and the mixture was stirred at 80℃ for 1.5 hours. The reaction mixture was concentrated to dryness, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 22 mg of an intermediate compound. 90 mg of sodium cyanoborohydride was suspended in 1 ml of tetrahydrofuran, and 0.66 ml of zinc chloride (1.0 M diethyl ether solution) was added dropwise. A suspension of 22 mg of the intermediate compound in 3 ml of tetrahydrofuran was added, and the mixture was stirred at room temperature for 2.5 hours. Water was added to the reaction mixture, and the mixture was made weakly alkaline with an aqueous saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 11 mg of the compound represented by the above formula.

FAB-MS(m/z):656$(M+H)^+$

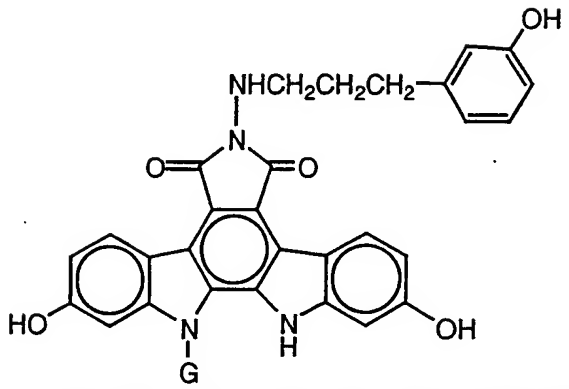
^{1}H-NMR(300MHz,DMSO-d_6,δppm):11.21(1H,s),9.80(1H,s),9.77(1H,s),8.86(1H,d,J=8.6Hz),8.78(1H,d,J=8.1Hz),7.82-7.95(1H,m),7.68-7.75(1H,m),7.33-7.43(1H,m),7.19(1H,s),7.00(1H,s),6.78-6.89(2H,m),6.22(1H,t,J=4.5Hz),5.97(1H,d,J=7.9Hz),5.86(1H,t,J=3.8Hz),5.33(1H,d,J=4.2Hz),5.29(1H,t,J=5.9Hz),5.11(1H,d,J=5.0Hz),4.91(1H,d,J=4.1Hz),4.42(2H,d,J=5.5Hz),4.33(2H,d,J=1.6Hz),3.99-4.09(1H,m),3.91(2H,m),3.72-3.80(1H,m),3.50(2H,m)

Example 26

Compound represented by the structural formula

【0065】

【Com. 37】



20 mg of Compound A and 20 mg of 3-(3-t-butyldimethylsilyloxyphenyl)propanal were suspended in 4 ml of anhydrous methanol, 20 ml of acetic acid was added, and the mixture was stirred at 80℃ for 8 hours. The reaction mixture was concentrated, and the concentrate was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 14 mg of an intermediate compound. This was suspended in 5 ml of methanol, 7.5 mg of sodium cyanoborohydride and 0.5 ml of a 10 % solution of hydrochloric acid in methanol were added, the mixture was stirred at room temperature for 2 hours, 0.5 ml of 2N hydrochloric acid was added, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed successively with water and saturated saline. The organic layer was dried and concentrated, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 12 mg of the compound represented by the above formula.

Rf value: 0.36 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS (m/z): 669 $(M+H)^+$

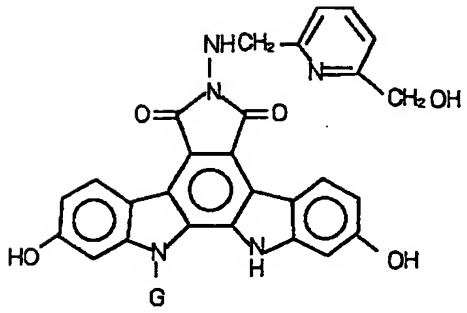
^{1}H-NMR (300MHz,DMSO-d_6,δppm)11.18(1H,s),9.65(3H,br),8.87(1H,d,J=8.1Hz), 8.79(1H,d,J=8.1Hz),7.17(1H,d,J=1.7Hz),7.02(1H,t,J=8.1Hz),6.98(1H,d,J=1.7Hz),6.81(2H,dt,J=1.7,5.7Hz),6.64(1H,d,J=8.1Hz),6.62(1H,s),6.57(1H,dd,J=1.8,8.1Hz),5.96(1H, d,J=8.1Hz),5.87(1H,br),5.74(1H,t,J=4.8Hz),5.35(1H,br),5.12(1H,br),4.92(1H,br),4.02(1H,d,J=10.8Hz),3.91(2H,m),3.79(1H,d,J=9.9Hz),3.51(2H,d,J=7.5Hz),3.02(2H,m),2.65 (2H,t,J=7.2Hz),1.72(2H,t,J=8.1Hz)

Example 27

Compound represented by the structural formula

【0066】

【Com. 38】



15 mg of Compound A and 6.9 mg of 6-hydroxymethylpyridine-2-carbaldehyde were suspended in 1 ml of anhydrous methanol, several drops of acetic acid were added, and the mixture was stirred at 80℃ for 5 hours. The reaction mixture was concentrated to dryness, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 5.2 mg of an intermediate compound. 68 mg of sodium cyanoborohydride was suspended in 2 ml of tetrahydrofuran, and 0.5 ml of zinc chloride (1.0 M diethyl ether solution) was added dropwise. A suspension of 5.2 mg of the intermediate compound in 1 ml of tetrahydrofuran was added, and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was made weakly alkaline with an aqueous saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 2.0 mg of the compound represented by the above formula.

Rf value: 0.29 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):656($M+H^+$)

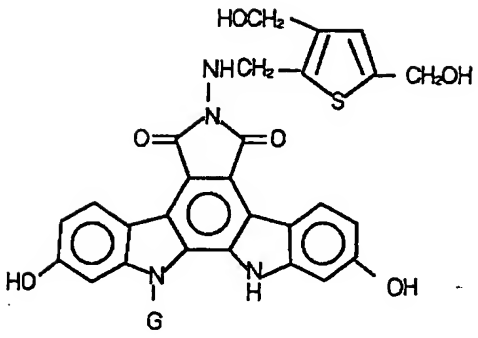
^{1}H-NMR(300MHz,DMSO-d_6 ,δppm):11.21(1H,s),9.80(1H,s),9.77(1H,s),8.86(1H,d, J=8.6Hz),8.78(1H,d,J=8.1Hz),7.82-7.95(1H,m),7.68-7.75(1H,m),7.33-7.43(1H,m), 7.19(1H,s),7.00(1H,s),6.78-6.89(2H,m),6.22(1H,t,J=4.5Hz),5.97(1H,d,J=7.9Hz),5.86 (1H,t,J=3.8Hz),5.33(1H,d,J=4.2Hz),5.29(1H,t,J=5.9Hz),5.11(1H,d,J=5.0Hz),4.91(1H,d ,J=4.1Hz),4.42(2H,d,J=5.5Hz),4.33(2H,d,J=1.6Hz),3.99-4.09(1H,m),3.91(2H,m),3.72-3.80(1H,m),3.50(2H,m)

Example 28

Compound represented by the structural formula

【0067】

【Com. 39】



40 mg of Compound A and 60 mg of 3,5-bis-(t-butyldimethylsilyloxymethyl) thiophene-2-carbaldehyde were suspended in 8 ml of anhydrous methanol, 40 ml of acetic acid was added, and the mixture was stirred at 80℃ for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 46 mg of an intermediate compound. This was suspended in 5 ml of methanol, 30 mg of sodium cyanoborohydride and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, and washed with water and an aqueous saturated sodium chloride solution. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 36 mg of the compound represented by the above formula.

Rf value: 0.24 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):690$(M)^+$

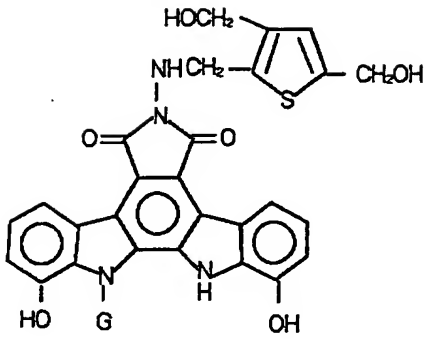
^{1}H-NMR(300MHz,DMSO-d_6,δp pm):11.19(1H,s),9.79(1H,s),9.76(1H,s),8.86(1H,d, J=8.4Hz),8.78(1H,d,J=8.4Hz),7.18(1H,d,J=1.8Hz),6.98(1H,d,J=1.8Hz),6.83(1H,s),6.82(2H,dt,J=1.8,8.4Hz),5.99(1H,t,J=4.8Hz),5.97(1H,d,J=9.0Hz),5.87(1H,t,J=4.2Hz),5.35(1H,t,J=5.4Hz),5.33(1H,d,J=4.8Hz),5.12(1H,d,J=5.1Hz),4.96(1H,d,J=5.7Hz),4.94(1H,d,J=5.4Hz),4.49(4H,t,J=6.6Hz),4.34(2H,d,J=4.8Hz),4.03(1H,m),3.92(2H,m),3.77(1H,m),3.50(2H,m)

Example 29

Compound represented by the structural formula

【0068】

【Com. 40】



50 mg of Compound B and 60 mg of 3,5-bis-(t-butyldimethylsilyloxymethyl) thiophene-2-carbaldehyde were dissolved in 12 ml of anhydrous methanol/N,N-dimethylformamide (5:1), 50 ml of acetic acid was added, and the mixture was stirred overnight at 80℃. The reaction mixture was diluted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, dried, and concentrated. The residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was dissolved in 6 ml of a mixed solvent of tetrahydrofuran/methanol (2:1). 30 mg of sodium cyanoborohydride and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate, and washed with an aqueous saturated sodium bicarbonate solution and an aqueous saturated sodium chloride solution. The organic layer was dried and concentrated, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 37 mg of the compound represented by the above formula.

Rf value: 0.31 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):690$(M)^+$

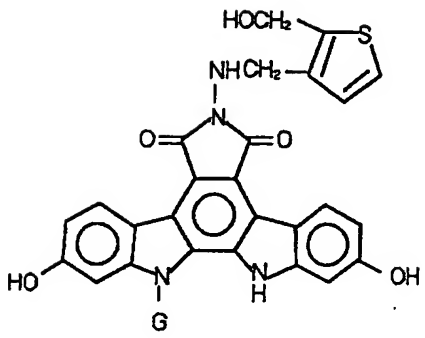
^{1}H-NMR(300MHz,DMSO-d_6, δppm):10.90(1H,s),10.37(1H,br),9.98(1H,br),8.69(1H, d,J=8.4Hz),8.52(1H,d,J=8.4Hz),7.19(2H,dt,J=1.5,8.4Hz),7.05(1H,d,J=8.6Hz),7.01(2H, t,J=8.4Hz),6.83(1H,s),6.04(1H,t,J=4.8Hz),5.42(1H,d,J=5.7Hz),5.35(2H,t,J=6.0Hz),5.2 1(1H,d,J=5.4Hz),4.95(1H,t,J=6.0Hz),4.91(1H,br),4.50(4H,t,J=5.7Hz),4.36(2H,d,J=5.4 Hz),4.00(2H,m),3.73(1H,m),3.62(2H,m),3.40(1H,m)

Example 30

Compound represented by the structural formula

【0069】

【Com. 41】



20 mg of Compound A and 20 mg of 2-hydroxymethylthiophene-3-carbaldehyde were dissolved in 4 ml of anhydrous methanol, 20 ml of acetic acid was added, and the mixture was stirred at 80℃ for 2 hours. The reaction mixture was concentrated under reduced pressure, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was dissolved in 3 ml of a mixed solvent of tetrahydrofuran/methanol (2:1). 30 mg of sodium cyanoborohydride and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 16 mg of the compound represented by the above formula.

Rf value: 0.49 (Kieselgel 60F_{254} made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):660$(M)^+$

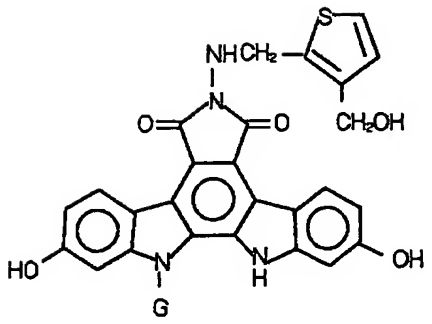
^{1}H-NMR(300MHz,DMSO-d_6 ,δppm):11.18(1H,s),9.79(1H,s),9.75(1H,s),8.86(1H, d,J=8.4Hz),8.78(1H,d,J=8.4Hz),7.30(1H,d,J=4.8Hz),7.17(1H,d,J=2.1Hz),7.09(1H,d,J= 5.4Hz),6.98(1H,d,J=2.1Hz),6.82(1H,dd,J=2.1,8.4Hz),6.80(1H,dd,J=2.1,8.4Hz),5.97(1 H,d,J=8.1Hz),5.92(1H,t,J=5.1Hz),5.86(1H,t,J=3.9Hz),5.37(1H,d,J=5.7Hz),5.33(1H,d,J =4.5Hz),5.12(1H,d,J=4.8Hz),4.93(1H,d,J=4.8Hz),4.76(2H,d,J=5.7Hz),4.20(2H,d,J=5.1 Hz),4.00(1H,m),3.91(2H,s),3.77(1H,m),3.50(2H,m)

Example 31

Compound represented by the structural formula

【0070】

【Com. 42】



30 mg of Compound A and 30 mg of 3-t-butyldimethylsilyloxymethylthiophene-2-carbaldehyde were dissolved in 5 ml of anhydrous methanol, 30 ml of acetic acid was added, and the mixture was stirred 80℃ for 2 hours. The reaction mixture was concentrated under reduced pressure, and the residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was suspended in 3 ml of methanol. 30 mg of sodium cyanoborohydride and 300 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 1 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 24 mg of the compound represented by the above formula.

Rf value: 0.40 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):660$(M)^+$

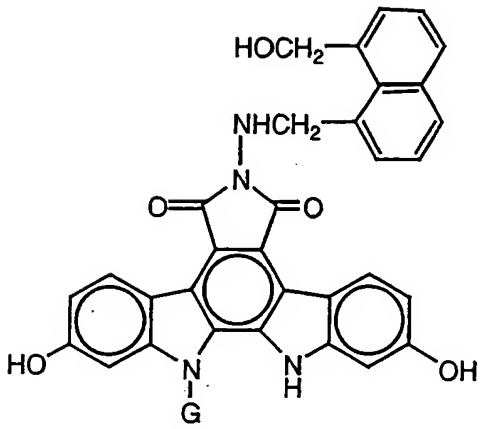
^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):11.19(1H,s),9.78(1H,s),9.75(1H,s),8.85(1H,d, J=8.7Hz),8.78(1H,d,J=9.0Hz),7.31(1H,d,J=4.8Hz),7.18(1H,d,J=1.8Hz),6.99(1H,d,J=4.8Hz),6.97(1H,d,J=1.8Hz),6.81(2H,dd,J=1.8,9.0Hz),6.06(1H,t,J=4.8Hz),5.97(1H,d,J=8.7Hz),5.86(1H,t,J=3.9Hz),5.33(1H,d,J=4.5Hz),5.12(1H,d,J=4.5Hz),4.99(1H,t,J=5.4Hz), 4.93(1H,d,J=5.1Hz),4.53(2H,d,J=5.7Hz),4.38(2H,d,J=4.8Hz),4.02(1H,m),3.91(2H,m), 3.77(1H,m),3.50(2H,m)

Example 32

Compound represented by the structural formula

【0071】

【Com. 43】



35 mg of Compound A and 60 mg of 8-t-butyldimethylsilyloxymethyl-1-naphthoaldehyde were suspended in 2 ml of methanol, everal drops of acetic acid was added, and the mixture was stirred at 60℃ for 2 hours. The reaction mixture was concentrated, and the resulting solid was washed with chloroform to obtain 32.5 mg of an intermediate compound. 68 mg of sodium cyanoborohydride was suspended in 3 ml of tetrahydrofuran, and 0.5 ml of zinc chloride (1.0 M diethyl ether solution) was added dropwise. A suspension of 32.5 mg of the intermediate compound in 2 ml of tetrahydrofuran was added thereto, and the mixture was stirred at room temperature for 2 hours, saturated saline was added, and the mixture was extracted with a mixed solvent of ethyl acetate/methyl ethyl ketone. The organic layer was dried and concentrated, the residue was dissolved in 1.5 ml of tetrahydrofuran, and 0.5 ml of tetrabutylammonium fluoride was added. The mixture was stirred at room temperature for 1.5 hours, diluted with a mixed solvent of ethyl acetate/methyl ethyl ketone, and washed successively with water and saturated saline. The organic layer was dried and concentrated, and the concentrate was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 3.3 mg of the compound represented by the above formula.

FAB-MS (m/z): 705 $(M+H)^+$

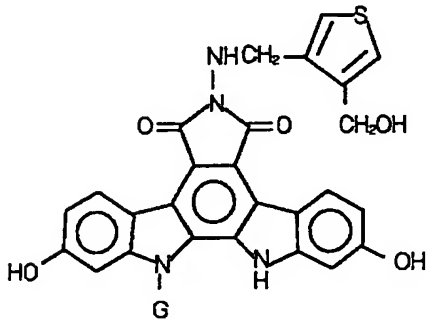
^{1}H-NMR (300MHz,DMSO-d_6,δp pm)11.16(1H,s),8.84(1H,d,J=7.9Hz),8.76(1H,d,J=7.9Hz),7.87(2H,d,J=7.4Hz),7.68(1H,d,J=7.4Hz),7.58(1H,d,J=7.4Hz),7.49(1H,d,J=7.4Hz),7.39(1H,t,J=7.4Hz),7.15(1H,s),6.97(1H,s),6.80(2H,t,J=7.9Hz),5.86-6.00(3H,m),5.42(2H,s),4.85(2H,d,J=4.2Hz),4.80-5.50(4H,br),3.72-4.05(4H,m),3.45-3.59(2H,m)

Example 33

Compound represented by the structural formula

【0072】

【Com. 44】



30 mg of Compound A and 30 mg of 4-t-butyldimethylsilyloxythiophene-3-carbaldehyde were suspended in 6 ml of methanol, 30 ml of acetic acid was added, and the mixture was stirred 80℃ for 2 hours. The reaction mixture was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness, and the residue was dissolved in 5 ml of a mixed slovent of tetrahydrofuran/methanol (2:1). 20 mg of sodium cyanoborohydride and 200 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, dried and concentrated. The residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 15 mg of the compound represented by the above formula.

Rf value: 0.47 (Kieselgel 60F_{254} made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):661$(M+H)^+$

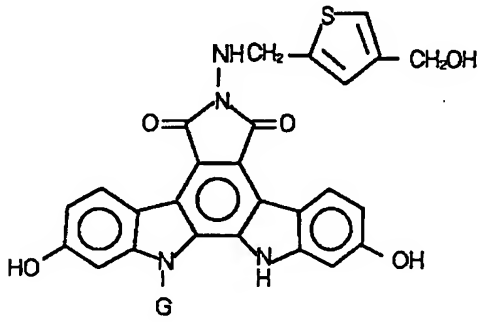
^{1}H-NMR(300MHz,DMSO-d_6 ,δp pm):11.19(1H,s),9.79(1H,s),9.76(1H,s),8.86(1H,d, J=8.7Hz),8.78(1H,d,J=8.7Hz),7.43(1H,d,J=3.3Hz),7.30(1H,d,J=3.6Hz),7.17(1H,d,J=2.1Hz),6.98(1H,d,J=2.1Hz),6.83(1H,dd,J=2.1,8.7Hz),6.81(1H,dd,J=2.1,8.7Hz),6.04(1H,t,J=5.1Hz),5.97(1H,d,J=9.0Hz),5.87(1H,t,J=3.6Hz),5.34(1H,d,J=3.9Hz),5.12(1H,d,J=5.1Hz),5.10(1H,t,J=5.1Hz),4.92(1H,d,J=4.5Hz),4.67(2H,d,J=5.4Hz),4.23(2H,d,J=4.2Hz),4.01(1H,m),3.92(2H,s),3.77(1H,m),3.50(2H,m)

Example 34

Compound represented by the structural formula

【0073】

【Com. 45】



38 mg of Compound A and 25 mg of 4-hydroxymethylthiophene-2-carbaldehyde were suspended in 7 ml of anhydrous methanol, 45 ml of acetic acid was added, and the mixture was stirred at 80℃ for 7 hours. The reaction mixture was concentrated under reduced pressure, and 38 mg of crystals obtained by filtration from methanol/chloroform. The crystals were dissolved in 10 ml of tetrahydrofuran/methanol (4:1), 13 mg of sodium cyanoborohydride and 0.5 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed with an aqueous saturated sodium chloride solution, dried and concentrated. The residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 21.7 mg of the compound represented by the above formula.

Rf value: 0.24 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):660(M^+)

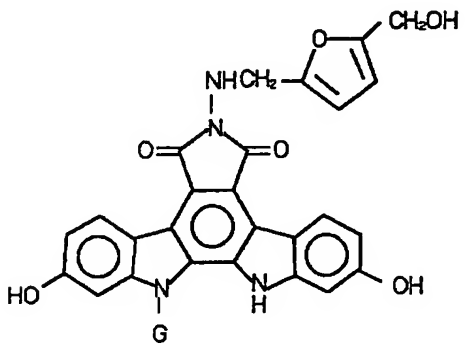
^{1}H-NMR(300MHz,DMSO-d_6,δp pm):11.19(1H,s),9.77(2H,br),8.86(1H,d,J=8.6Hz), 8.78(1H,d,J=8.6Hz),7.17(1H,s),7.14(1H,d,J=1.8Hz),6.98(2H,m),6.81(2H,dt,J=1.8,6.9 Hz),6.12(1H,t,J=5.1Hz),5.97(1H,d,J=8.1Hz),5.87(1H,s),5.35(1H,d,J=1.8Hz),5.13(1H,d ,J=2.4Hz),5.01(1H,t,J=5.4Hz),4.93(1H,d,J=3.6Hz),4.40(2H,d,J=4.5Hz),4.34(2H,d,J=4. 8Hz),4.00(1H,dd,J=2.1,11.6Hz),3.91(2H,s),3.79(1H,m),3.51(2H,br)

Example 35

Compound represented by the structural formula

【0074】

【Com. 46】



107 mg of Compound A and 126 mg of 5-hydroxymethylfurfural were suspended in 2 ml of methanol, several drops of acetic acid were added, and the mixture was stirred overnight at 80℃. The reaction mixture was concentrated and the obtained solid was washed with chloroform. The solid was dissolved in 5 ml of a mixed solvent of methanol/tetrahydrofuran (1:2), 62.8 mg of sodium cyanoborohydride and 5 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with a mixed slovent of ethyl acetate/methyl ethyl ketone, and washed with water and an aqueous saturated sodium chloride solution. The organic layer was dried, concentrated, put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 103 mg of the compound represented by the above formula.

FAB-MS(m/z):644$(M)^+$

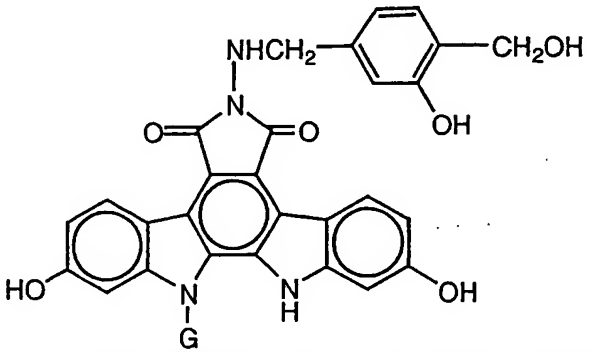
^{1}H-NMR(300MHz,DMSO-d_6 ,δppm):11.19(1H,s),9.77(2H,br),8.85(1H,d,J=8.5Hz), 8.77(1H,d,J=8.6Hz),7.18(1H,d,J=2.1Hz),6.98(1H,d,J=1.7Hz),6.75-6.86(2H,m),6.31 (1H,d,J=3.1Hz),6.15(1H,d,J=3.1Hz),6.03(1H,t,J=4.7Hz),5.97(1H,d,J=8.3Hz),5.87(1H,t ,J=3.6Hz),5.34(1H,d,J=3.9Hz),5.08-5.15(2H,m),4.93(1H,d,J=4.5Hz),4.28(2H,d, J=5.6Hz),4.20(2H,d,J=4.7Hz),3.72-4.05(4H,m),3.45-3.55(2H,m)

Example 36

Compound represented by the structural formula

【0075】

【Com. 47】



39 mg of Compound A and 33 mg of 3-hydroxy-4-hydroxymethylbenzaldehyde were suspended in 8 ml of methanol, 150μl of acetic acid was added, and the mixture was stirred at room temperature over a period of three nights. The reaction mixture was

filtered, and the resulting solid was washed with chloroform. The solid was dissolved in 5 ml of a mixed solvent of methanol/tetrahydrofuran (1:2), 9 mg of sodium cyanoborohydride and several drops of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated to dryness, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 3.5 mg of the compound represented by the above formula.

FAB-MS (m/z): 670 (M^+)

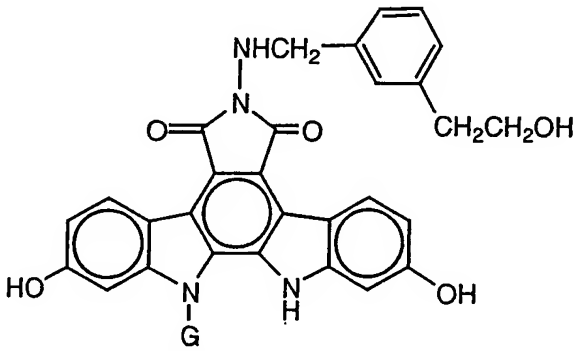
^{1}H-NMR (300MHz,DMSO-d_6,δp pm)11.18(1H,s),9.77(1H,s),9.76(1H,s),9.28(1H,br), 8.87(1H,d,J=8.5Hz),8.78(1H,d,J=8.5Hz),7.18(1H,d,J=7.9Hz),7.17(1H,s),6.97(1H,d,J= 2.0Hz),6.77-6.93(4H,m),5.96(1H,d,J=8.2Hz),5.92(1H,t,J=5.0Hz),5.86(1H,t,J=3.2Hz), 5.33(1H,d,J=4.3Hz),5.12(1H,d,J=4.6Hz),4.92(1H,d,J=5.0Hz),5.83(1H,br),4.41(2H,d,J =3.2Hz),4.14(2H,d,J=5.0Hz),4.00(1H,m),3.90(2H,m),3.78(1H,m),3.50(2H,m)

Example 37

Compound represented by the structural formula

【0076】

【Com. 48】

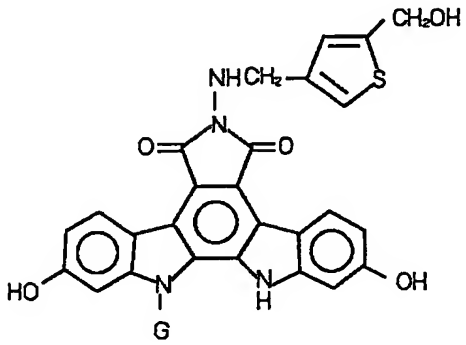


30 mg of Compound A and 24.9 mg of 3-(2-hydroxyethyl)benzaldehyde were suspended in 1 ml of methanol, several drops of acetic acid was added, and the mixture was stirred at 80℃ for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was washed with chloroform. This was suspended in 2 ml of methanol, 9.0 mg of sodium cyanoborohydride and several drops of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated to dryness, and the residue was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 20.7 mg of the compound represented by the above formula.

FAB-MS (m/z): 669 $(M+H)^+$

^{1}H-NMR (300MHz,DMSO-d_6,δp pm)11.18(1H,s),9.78(1H,s),9.75(1H,s),8.87 (1H,d,J=8.5Hz),8.79(1H,d,J=8.6Hz),7.36(1H,s),7.32(1H,d,J=7.6Hz),7.15-7.25 (2H,m), 7.07(1H,d,J=7.6Hz),6.97(1H,d,J=2.0Hz),6.75-6.85(2H,m),6.02(1H,d,J=5.2Hz),5.96 (1H,d,J=8.2Hz),5.86(1H,t,J=3.3Hz),5.33(1H,d,J=4.3Hz),5.11(1H,d,J=4.9Hz),4.90(1H, d,J=5.4Hz),4.61(1H,t,J=5.3Hz),4.23(2H,d,J=4.5Hz),3.72-4.05(4H,m),3.45-3.60(4H,m), 2.69(2H,t,J=7.3Hz)

Example 38
Compound represented by the structural formula
【0077】
【Com. 49】



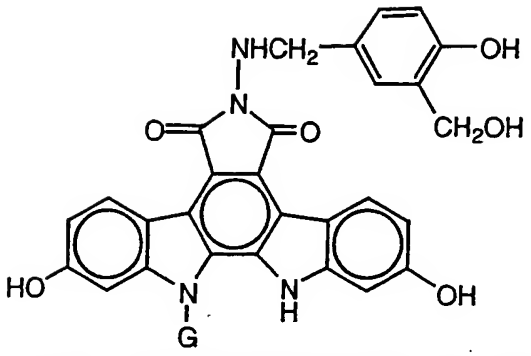
40 mg of Compound A and 40 mg of 5-hydroxymethylthiophene-3-carbaldehyde were suspended in 8 ml of methanol, 40 ml of acetic acid was added, and the mixture was stirred at 80℃ for 3 hours. The reaction mixture was cooled to room temperature, chloroform was added, and the resulting powder was obtained by filtration. This was suspended in 5 ml of methanol, 20 mg of sodium cyanoborohydride and 200 ml of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with a mixed slovent of ethyl acetate/methyl ethyl ketone, washed with water and an aqueous saturated sodium chloride solution, dried, and concentrated. The residue was put on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 21 mg of the compound represented by the above formula.

Rf value: 0.29 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent: acetonitrile: tetrahydrofuran: toluene: water: acetic acid = 4:2:2:0.5:0.1)

FAB-MS(m/z):660(M^+)

^{1}H-NMR(300MHz,DMSO-d_6 ,δp p m):11.19(1H,s),9.80(2H,br),8.86(1H,d,J=9.0Hz), 8.79(1H,d,J=8.7Hz),7.34(1H,s),7.17(1H,d,J=1.5Hz),7.04(1H,s),6.97(1H,d,J=1.5Hz),6. 82(1H,dd,J=1.5,9.0Hz),6.80(1H,dd,J=8.7,1.5Hz),5.97(2H,t,J=5.1Hz),5.87(1H,br),5.40(1H,t,J=6.0Hz),5.35(1H,br),5.13(1H,s),4.91(1H,d,J=3.9Hz),4.57(2H,d,J=4.2Hz),4.20(2 H,d,J=4.8Hz),3.88-4.10(3H,m),3.78(1H,m),3.50(2H,m)

Example 39
Compound represented by the structural formula
【0078】
【Com. 50】



38 mg of Compound A and 91 mg of 3-hydroxymethyl-4-hydroxybenzaldehyde were dissolved in 2 ml of N,N-dimethylformamide, three drops of acetic acid was added, and the mixture was stirred at 80℃ for 3 hour. The reaction mixture was concentrated under reduced pressure, and the residue was washed with chloroform. This was suspended in 3 ml of methanol, 40 mg of sodium cyanoborohydride and several drops of a 10 % solution of hydrochloric acid in methanol were added, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was placed on a Sephadex LH-20 column for chromatography and eluted with methanol. Fractions containing the desired compound were concentrated to dryness to obtain 8.9 mg of the compound represented by the above formula.

Rf value: 0.15 (Kieselgel $60F_{254}$ made by Merck Co., developing solvent ; acetonitrile:tetrahydrofuran:toluene:water:acetic acid=4:2:2:0.5:0.1)

FAB-MS (m/z):

^{1}H-NMR (300MHz,DMSO-d_6,δp pm)11.19(1H,s),9.75(1H,br),9.74(1H,br),9.23(1H,br),8.87(1H,d,J=8.6Hz),8.79(1H,d,J=8.6Hz),7.37(1H,s),7.12-7.20(2H,m),6.98(1H,d,J=2.1Hz),6.75-6.85(2H,m),6.70(1H,d,J=8.3Hz),5.97(1H,d,J=8.3Hz),5.86(1H,t,J=4.4Hz),5.76(1H,t,J=5.3Hz),5.33(1H,d,J=4.4Hz),5.10(1H,d,J=3.4Hz),4.89-4.98(2H,m),4.44(2H,d,J=4.5Hz),3.72-4.15(6H,m),3.48-3.55(2H,m)

【0079】

【Effect of the Invention】

The compounds of the invention have excellent antitumor effect, and are useful as antitumor agents in the field of medicine.

【0080】

Continued from the front page

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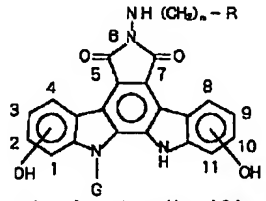
(54)【発明の名称】　抗腫瘍性インドロピロロカルバゾール誘導体

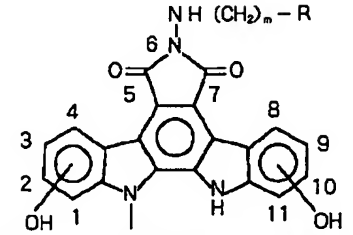
(57)【要約】
【課題】新規抗腫瘍剤の創製。
【解決手段】一般式
【化１】



[I]

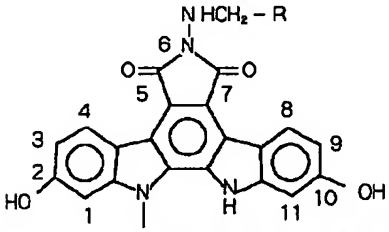
[式中、Ｒはヒドロキシ基、低級アルコキシ基、ヒドロキシ低級アルキル基及びヒドロキシ低級アルケニル基からなる群から選ばれる１又は２個の置換基を有するフェニル基、ナフチル基、ピリジル基、フリル基又はチエニル基（但し、置換基として低級アルコキシ基を有する場合は、同時にヒドロキシ基、低級アルコキシ基、ヒドロキシ低級アルキル基及びヒドロキシ低級アルケニル基からなる群から選ばれるもう一つの置換基を有する）を示し、ｍは１～３の整数を示し、Ｇはβ－Ｄ－グルコピラノシル基を示し、インドロピロロカルバゾール環上のヒドロキシ基の置換位置は１位と１１位又は２位と１０位である]で表される化合物又はその医薬上許容される塩。

【特許請求の範囲】
【請求項１】一般式
【化１】



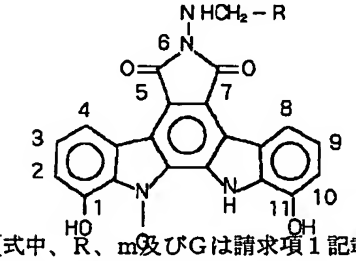
[I]

［式中、Ｒはヒドロキシ基、低級アルコキシ基、ヒドロキシ低級アルキル基及びヒドロキシ低級アルケニル基からなる群から選ばれる１又は２個の置換基を有するフェニル基、ナフチル基、ピリジル基、フリル基又はチエニル基（但し、置換基として低級アルコキシ基を有する場合は、同時にヒドロキシ基、低級アルコキシ基、ヒドロキシ低級アルキル基及びヒドロキシ低級アルケニル基からなる群から選ばれるもう一つの置換基を有する）を示し、ｍは１～３の整数を示し、Ｇはβ－Ｄ－グルコピラノシル基を示し、インドロピロロカルバゾール環上のヒドロキシ基の置換位置は１位と１１位又は２位と１０位である］で表される化合物又はその医薬上許容される塩。
【請求項２】一般式
【化２】



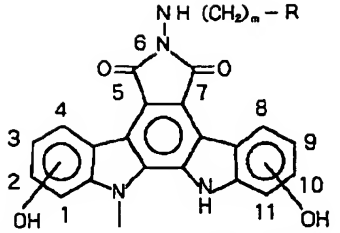
[I－a]

［式中、Ｒ、ｍ及びＧは請求項１記載の意味を有する］で表される請求項１記載の化合物又はその医薬上許容される塩。
【請求項３】一般式
【化３】



[I－b]

［式中、Ｒ、ｍ及びＧは請求項１記載の意味を有する］で表される請求項１記載の化合物又はその医薬上許容される塩。
【請求項４】請求項１、２又は３に記載の化合物又はその医薬上許容される塩を含有することを特徴とする抗腫瘍剤。
【発明の詳細な説明】
【０００１】
【産業上の利用分野】本発明は医薬の分野で有用であり、さらに詳細には腫瘍細胞の増殖を阻害し、抗腫瘍効果を発揮する新規なインドロピロロカルバゾール誘導体、その製法及びその用途に関する。
【０００２】
【従来の技術】癌化学療法の分野においては、すでに多数の化合物が医薬として実用化されている。しかしながら、様々な種類の腫瘍に対してその効果は必ずしも充分ではなく、またこれらの薬剤に対する腫瘍細胞の耐性の問題も臨床上の使用法を複雑にしている［第４７回日本癌学会総会記事、１２～１５頁（１９８８年）参照］。
【０００３】このような状況下、癌治療の分野においては常に新規制癌物質の開発が求められている。特に、既存の制癌物質に対する耐性を克服し、既存の制癌物質が充分に効果を発揮できない種類の癌に対して有効性を示す物質が必要とされている。
【０００４】このような現状に鑑み、本発明者らは広く微生物代謝産物をスクリーニングした結果、抗腫瘍活性を有する新規な化合物ＢＥ－１３７９３Ｃ（１２，１３－ジヒドロ－１，１１－ジヒドロキシ－５Ｈ－インドロ［２，３－ａ］ピロロ［３，４－ｃ］カルバゾール－５，７（６Ｈ）－ジオン）を見出した（ヨーロッパ特許公開公報０３８８９５６Ａ２参照］。
【０００５】その後、ＢＥ－１３７９３Ｃに化学修飾を加えて更に優れた抗腫瘍活性を有する化合物を創製することを試み、先の特許出願（ヨーロッパ特許公開公報０５２８０３０Ａ１、ヨーロッパ特許公開公報０５４５１９５Ａ１、ＷＯ９５／３０６８２及びＷＯ９６／０４２９３）において開示した。
【０００６】
【発明が解決しようとする課題】先の特許出願において開示したインドロピロロカルバゾール系の抗腫瘍性物質に化学修飾を施し、更に優れた抗腫瘍活性を有する化合物を創製することが本発明が解決しようとする課題である。
【０００７】
【課題を解決するための手段】本発明者等は、上記課題を解決すべく、インドロピロロカルバゾール誘導体を広く合成し、抗腫瘍活性について検討した結果、後記一般式［Ｉ］で表される化合物が、上記、先の特許出願において開示したインドロピロロカルバゾール化合物よりも更に優れた抗腫瘍作用を示すことを見いだして本発明を完成した。
【０００８】即ち、本発明は一般式
【０００９】
【化４】



[I]

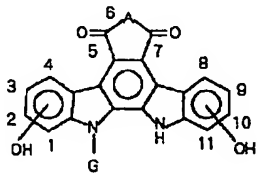
[式中、Rはヒドロキシ基、低級アルコキシ基、ヒドロキシ低級アルキル基及びヒドロキシ低級アルケニル基からなる群から選ばれる１又は２個の置換基を有するフェニル基、ピリジル基、フリル基又はチエニル基（但し、置換基として低級アルコキシ基を有する場合は、同時にヒドロキシ基、低級アルコキシ基、ヒドロキシ低級アルキル基及びヒドロキシ低級アルケニル基からなる群から選ばれるもう一つの置換基を有する）を示し、ｍは１～３の整数を示し、Ｇはβ－Ｄ－グルコピラノシル基を示し、インドロピロロカルバゾール環上のヒドロキシ基の置換位置は１位と１１位又は２位と１０位である］で表される化合物又はその医薬上許容される塩及びその用途に関するものである。

【００１０】次に本発明化合物の製造法について説明する。

【００１１】本発明のインドロピロロカルバゾール誘導体は、ヨーロッパ特許公開公報０５２８０３０Ａ１、ヨーロッパ特許公開公報０５４５１９５Ａ１、ＷＯ９５／３０６８２及びＷＯ９６／０４２９３に記載の公知化合物である、一般式

【００１２】

【化５】



[II]

［式中、ＡはＮＨ又はＨをを示し、Ｇは前記の意味を有する］で表される化合物に、一般式

【００１３】

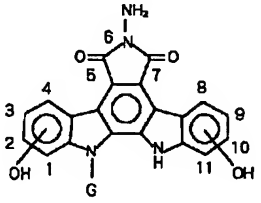
【化６】

[III]

［式中、Ｒ及びｍは前記の意味を有する］で表される化合物を反応させるか、一般式

【００１４】

【化７】



[IV]

［式中、Ｇは前記の意味を有する］で表される化合物と、一般式

【００１５】

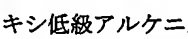
【化８】

[V]

［式中、Ｒ１はＲと同様の意味を有するかＲに有する水酸基が保護された基を意味し、ｍは前記の意味を有する］で表される化合物を縮合させ、次いで還元し、そして必要に応じて保護基の除去を行うことにより製造するか、又は一般式ＩＶ］の化合物に、一般式

【００１６】

【化９】



[VI]

［式中、Ｌは脱離基を示し、Ｒ１及びｍは前記と同様の意味を有する］で表される化合物を反応させ、、そして必要に応じて保護基の除去を行うことにより製造することができる。

【００１７】一般式［ＩＩ］で表される化合物と一般式［ＩＩＩ］で表される化合物との反応は化学の分野で広く知られたイミド又は酸無水物とヒドラジン誘導体との反応である。この反応は、通常反応に悪影響を及ぼさない溶媒、例えばテトラヒドロフラン、Ｎ，Ｎ－ジメチルホルムアミド等を用いて行うことができ、化合物［ＩＩＩ］の使用量は化合物［ＩＩ］に対して通常少過剰から５モル当量であるが、必要に応じて大過剰用いて行うこともできる。

【００１８】反応温度は通常－５０℃～溶媒の沸点の範囲であり、必要に応じてこれ以上又はこれ以下の温度を選択することもできる。反応時間は通常３０分～２日間の範囲であるが必要に応じてこれ以上又はこれ以下の時間で行うことができる。

【００１９】また一般式［ＩＶ］で表される化合物と一般式［Ｖ］で表される化合物を縮合させ、ついで還元して化合物［Ｉ］を製造する反応は、同一の反応系で行うことができるが、場合により中間生成物であるシッフ塩基を一旦単離することもできる。すなわち通常、化合物［ＩＶ］と化合物［Ｖ］を適当な溶媒中で混合し、次いで還元剤を添加することにより行うことができる。この際、酢酸、塩酸等の酸の存在下に反応を行うことが好ましい。ここで使用できる溶媒としては、例えばメタノール、エタノール等のアルコール系溶媒、Ｎ，Ｎ－ジメチルホルムアミド等の非プロトン性極性溶媒等を挙げることができる。シッフ塩基の還元は、シアノ水素化ほう素ナトリウム等の水素化金属錯体等を用いて行うことができるが、また接触還元法により行うこともできる。

【００２０】また一般式［ＩＶ］の化合物と一般式［ＶＩ］の反応は、アミンのアルキル化反応であり、公知の方法、例えばアルキルハライド、アルキルメシレート又はアルキルトシレート等との反応等により行うことができる。

【００２１】また、上記反応の生成物は有機合成化学の分野における公知の方法、例えば沈澱法、溶媒抽出法、再結晶、クロマトグラフィー法等により精製することができる。

【００２２】更に本発明には、上記方法で得られる化合物の医薬上許容される塩も包含される。このような塩としては例えばカリウム、ナトリウム等のアルカリ金属との塩、例えばカルシウム等のアルカリ土類金属との塩、又は例えばエチルアミン及びアルギニン等の塩基性有機化合物との塩、例えば塩酸、硫酸等の無機酸との塩又は例えば酢酸、クエン酸、マレイン酸等の有機酸との塩を挙げることができる。

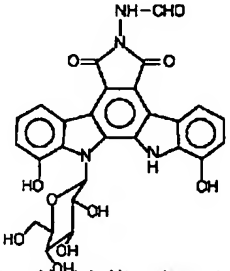
【００２３】本発明の式［Ｉ］で表される化合物は、優れた抗腫瘍作用を示す。

【００２４】ヒト胃癌ＭＸ－１に対する効果

予めヌードマウス皮下に移植し、増殖させたＭＸ－１固型腫瘍を細切し、その３ｍｍ角を被験マウス皮下に移植した。移植後、腫瘍が０．３ｃｍ^{3}に増殖した時点より各量の試験薬物をマウス尾静脈に１日１回５日間連続注射し、２日休薬後更に５日間注射（治療スケジュール：５／ｗ×２）又は３～４日毎に４回（治療スケジュール：２／ｗ×２）注射し治療した。治療開始２０日後又は３２日後に腫瘍の長径（Ｌ）及び短径（Ｗ）を測定し、その体積（Ｖ）を求めた（Ｖ＝１／２×Ｌ×Ｗ^2）。この体積より腫瘍増殖阻害率を算出し、腫瘍増殖を７５％抑制する投与総量（ＧＩＤ$_{75}$，ｍｇ／ｋｇ）を求めた。対照化合物としては、式

【００２５】

【化１０】



の化合物を用いた。結果を第１表に示した。

【００２６】

【表１】

第１表　本発明化合物のヒト胃癌MX-1に対する効果

供試化合物	治療スケジュール	GID_{75} (mg／kg total)
実施例3	2／w×2	＜90
実施例5	5／w×2	＜90
実施例10	5／w×2	＜90
実施例12	2／w×2	97
実施例14	2／w×2	＜12
実施例27	2／w×2	＜4.5
実施例28	2／w×2	＜36
実施例30	5／w×2	16
実施例31	5／w×2	＜30
実施例33	5／w×2	＜30
実施例35	5／w×2	82
実施例36	5／w×2	＜30
実施例37	5／w×2	32
実施例38	5／w×2	19
実施例39	2／w×2	＜30
対照化合物	5／w×2	1900

本発明により提供される化合物は、対照化合物に比べ、上記の薬理試験結果に示される如く更に優れた抗腫瘍作用を示す。

【００２７】上記の薬理試験の結果から明らかなように、本発明の化合物は優れた抗腫瘍作用を示し、抗腫瘍剤として疾病の予防・治療のため、殊に癌の処置のために有用である。　本発明化合物を抗腫瘍剤として使用する際の投与形態としては各種の形態を選択でき、例えば錠剤、カプセル剤、散剤、顆粒剤若しくは液剤等の経口剤、又は例えば溶液若しくは懸濁液等の殺菌した液状の非経口剤が挙げられる。

【００２８】固体の製剤は、そのまま錠剤、カプセル剤、顆粒剤又は粉末の形態として製造することもできるが、適当な添加物を使用して製造することもできる。そのような添加物としては、例えば乳糖若しくはブドウ糖等の糖類、例えばトウモロコシ、小麦若しくは米等の澱粉類、例えばステアリン酸等の脂肪酸、例えばメタケイ酸アルミン酸マグネシウム若しくは無水リン酸カルシウム等の無機塩、例えばポリビニルピロリドン若しくはポリアルキレングリコール等の合成高分子、例えばステアリン酸カルシウム若しくはステアリン酸マグネシウム等の脂肪酸塩、例えばステアリルアルコール若しくはベンジルアルコール等のアルコール類、例えばメチルセルロース、カルボキシメチルセルロース、エチルセルロース

若しくはヒドロキシプロピルメチルセルロース等の合成セルロース誘導体、その他、水、ゼラチン、タルク、植物油、アラビアゴム等通常用いられる添加物が挙げられる。

【００２９】これらの錠剤、カプセル剤、顆粒剤及び粉末等の固形製剤は一般的には０．１～１００重量%、好ましくは５～１００重量%の有効成分を含む。

【００３０】液状製剤は、水、アルコール類又は例えば大豆油、ピーナツ油若しくはゴマ油等の植物由来の油等液状製剤において通常用いられる適当な添加物を使用し、懸濁液、シロップ剤若しくは注射剤等の形態として製造される。

【００３１】特に、非経口的に筋肉内注射、静脈内注射又は皮下注射で投与する場合の適当な溶剤としては、例えば注射用蒸留水、塩酸リドカイン水溶液（筋肉内注射用）、生理食塩水、ブドウ糖水溶液、エタノール、ポリエチレングリコール、静脈内注射用液体（例えばクエン酸及びクエン酸ナトリウム等の水溶液）若しくは電解質溶液（点滴静注及び静脈内注射用）等、又はこれらの混合溶液が挙げられる。

【００３２】これらの注射剤は予め溶解したものの他、粉末のまま或いは適当な添加物を加えたものを用時溶解する形態もとり得る。これらの注射液は、通常０．１～１０重量%、好ましくは１～５重量%の有効成分を含む。

【００３３】また、経口投与の懸濁剤又はシロップ剤等の液剤は、０．５～１０重量%の有効成分を含む。

【００３４】本発明の化合物の実際に好ましい投与量は、使用される化合物の種類、配合された組成物の種類、適用頻度及び治療すべき特定部位、宿主及び腫瘍によって変化することに注意すべきである。例えば、１日当りの成人１人当りの投与量は、経口投与の場合、１０ないし５００ｍｇであり、非経口投与、好ましくは静脈内注射の場合、１日当り１０ないし１００ｍｇである。なお、投与回数は投与方法及び症状により異なるが、１回ないし５回である。また、隔日投与、隔々日投与などの間歇投与等の投与方法も用いることができる。

【００３５】

【発明の実施の形態】

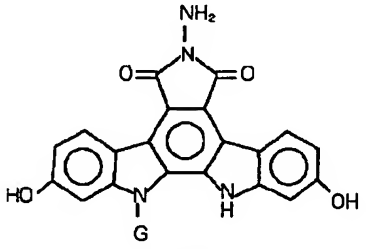
【００３６】

【実施例】以下に実施例を挙げて本発明をより具体的に説明するが、本発明はこれら実施例のみに限定されるものではない。

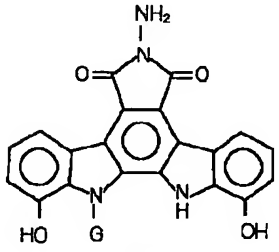
【００３７】なお、実施例において原料として用いた以下の構造式を有する化合物を下記のとおり略称する。

【００３８】

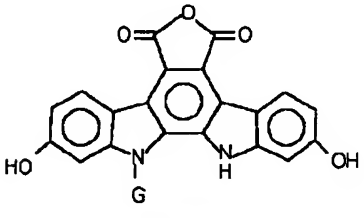
【化１１】



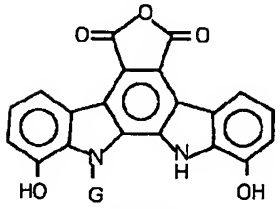
化合物 A



化合物 B



化合物 C



化合物 D

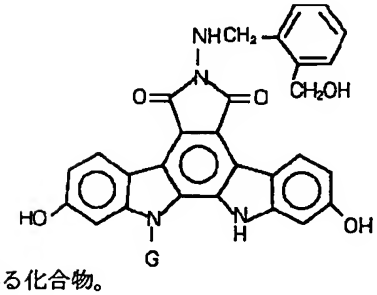
式中、Gはβ－D－グルコピラノシル基を示す。以下の実施例において同じ。

実施例１

構造式

【００３９】

【化１２】



で表される化合物。

【００４０】化合物Ａ２５ｍｇと（２－ｔ－ブチルジメチルシリルオキシメチル）ベンジルブロミド９０ｍｇをＮ，Ｎ－ジメチルホルムアミド１ｍｌに溶解し、室温で一晩撹拌した。反応液を減圧乾固した残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮し、再びセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、残渣をクロロホルムで洗浄することにより、表題の式で表される化合物３．６ｍｇを得た。

ＦＡＢ－ＭＳ（ｍ／ｚ）：６５５（Ｍ＋Ｈ）$^{+}$

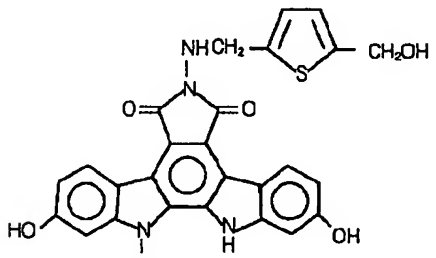
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１９（１Ｈ，ｓ），９．７８（１Ｈ，ｓ），９．７５（１Ｈ，ｓ），８．８６（１Ｈ，ｄ，Ｊ＝８．６Ｈｚ），８．７８（１Ｈ，ｄ，Ｊ＝８．２Ｈｚ），７．４４（１Ｈ，ｄ，Ｊ＝７．２Ｈｚ），７．３７（１Ｈ，ｄ，Ｊ＝７．６Ｈｚ），７．１３－７．２８（３Ｈ，ｍ），６．９８（１Ｈ，ｓ），６．７８－６．８８（２Ｈ，ｍ），５．９５－６．０５（２Ｈ，ｍ），５．８５（１Ｈ，ｂｒ），５．３３（１Ｈ，ｄ，Ｊ＝３．２Ｈｚ），５．１０－５．１７（２Ｈ，ｍ），４．９２（１Ｈ，ｄ，Ｊ＝４．０Ｈｚ），４．２８（２Ｈ，ｄ，Ｊ＝５．２Ｈｚ），３．７２－４．１０（４Ｈ，ｍ），３．４５－３．５５（２Ｈ，ｍ）

実施例２

構造式

【００４１】

【化１３】



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で表される化合物。化合物Ａ３０ｍｇと（５－ｔ－ブチルジメチルシリルオキシメチルチオフェン）－２－カルボキシアルデヒド３０ｍｇをメタノール６ｍｌに溶解し、酢酸３０ｍｌを加え、８０℃で４時間撹拌した。反応液を室温に冷却し、シアノ水素化ほう素ナトリウム２０ｍｇ、１０％塩酸メタノール溶液２００ｍｌを加え、室温で３０分間撹拌した。反応液を減圧乾固した残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物２７ｍｇを得た。

Ｒｆ値：０．３７（メルク社製，キーゼルゲル６０Ｆ$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６６０（Ｍ$^{+}$）

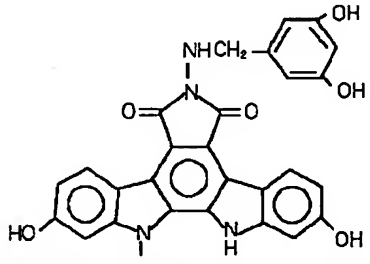
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１９（１Ｈ，ｓ），９．７９（１Ｈ，ｓ），９．７５（１Ｈ，ｓ），８．８６（１Ｈ，ｄ，Ｊ＝９．３Ｈｚ），８．７８（１Ｈ，ｄ，Ｊ＝９．０Ｈｚ），７．１７（１Ｈ，ｄ，Ｊ＝２．１Ｈｚ），６．９７（１Ｈ，ｄ，Ｊ＝２．１Ｈｚ），６．８９（１Ｈ，ｄ，Ｊ＝３．６Ｈｚ），６．８２（１Ｈ，ｄｄ，Ｊ＝２．１，９．３Ｈｚ），６．７９（１Ｈ，ｄｄ，Ｊ＝２．１，９．０Ｈｚ），６．７３（１Ｈ，ｄ，Ｊ＝３．３Ｈｚ），６．１０（１Ｈ，ｔ，Ｊ＝４．５Ｈｚ），５．９７（１Ｈ，ｄ，Ｊ＝８．１Ｈｚ），５．８６（１Ｈ，ｔ，Ｊ＝３．３Ｈｚ），５．３５（１Ｈ，ｔ，Ｊ＝６．０Ｈｚ），５．３２（１Ｈ，ｄ，Ｊ＝４．８Ｈｚ），５．１２（１Ｈ，ｄ，Ｊ＝４．８Ｈｚ），４．９２（１Ｈ，ｄ，Ｊ＝５．４Ｈｚ），４．５２（２Ｈ，ｄ，Ｊ＝５．７Ｈｚ），４．４０（２Ｈ，ｄ，Ｊ＝４．２Ｈｚ），４．０２（１Ｈ，ｍ），３．９１（２Ｈ，ｍ），３．７８（１Ｈ，ｍ），３．５０（２Ｈ，ｍ）

実施例３

構造式

【００４２】

【化１４】



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で表される化合物。化合物Ａ１００ｍｇと３，５－ジヒドロキシベンズアルデヒド１３１．２ｍｇをＮ，Ｎ－ジメチルホルムアミド１０ｍｌに溶解し、８０℃で４８時間撹拌した。反応液を減圧濃縮後、残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、９０．３ｍｇの中間化合物を得た。この中間化合物２０ｍｇをメタノール５ｍｌに懸濁し、シアノ水素化ほう素ナトリウム１０ｍｇ、１０％塩酸メタノール溶液　数滴を加え、室温で３０分間撹拌した。メタノールを減圧留去後、水を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄、乾燥濃縮した残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物１８ｍｇを得た。

Ｒｆ値：０．３０（メルク社製、キーゼルゲル６０Ｆ$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

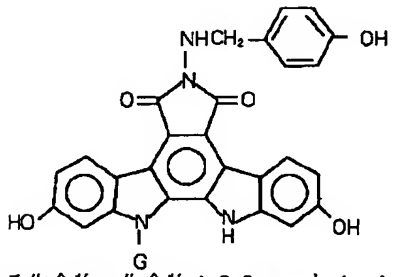
FAB－MS（m／z）：６５７（M+H+）
^{1}H－NMR（３００MHz，DMSO－d_6，δｐｐｍ）：１１．１９（１H，ｓ），９．７７（２H，ｂｒ），９．１１（２H，ｓ），８．８７（１H，ｄ，Ｊ＝８．６Hｚ），８．７９（１H，ｄ，Ｊ＝８．６Hｚ），７．１７（１H，ｓ），６．９７（１H，ｓ），６．７８～６．８４（２H，ｍ），６．３４（２H，ｓ），６．０６（１H，ｓ），５．９６（１H，ｄ，Ｊ＝８．３Hｚ），５．８３～５．８７（２H，ｍ），５．３４（１H，ｓ），５．１２（１H，ｓ），４．９２（１H，ｄ，Ｊ＝３．９Hｚ），４．０４（２H，ｄ，Ｊ＝４．５Hｚ），３．９１～３．９９（３H，ｍ），３．７５～３．８８（１H，ｍ），３．４９（２H，ｓ）

実施例４

構造式

【００４３】

【化１５】



で表される化合物。化合物Ａ３０ｍｇと４－ヒドロキシベンズアルデヒド１４ｍｇをメタノール６ｍｌに溶解し、酢酸１４ｍｌを加え、８０℃で２時間撹拌した。反応液を室温に冷却し、シアノ水素化ほう素ナトリウム２０mg、１０％塩酸メタノール溶液２００ｍｌを加え、室温で１時間撹拌した。反応液をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物３１ｍｇを得た。

Ｒｆ値：０．４１（メルク社製、キーゼルゲル６０F$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

FAB－MS（m／z）：６４０（M+）

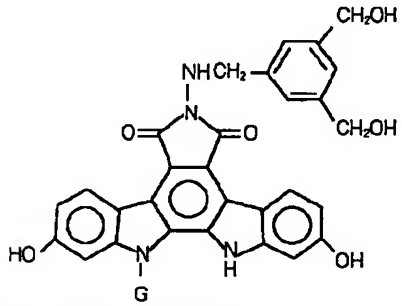
^{1}H－NMR（３００MHz，DMSO－d_6，δｐｐｍ）：１１．１７（１H，ｓ），９．７７（１H，ｓ），９．７４（１H，ｓ），９．２４（１H，ｓ），８．８６（１H，ｄ，Ｊ＝８．４Hｚ），８．７８（１H，ｄ，Ｊ＝８．４Hｚ），７．２５（２H，ｄ，Ｊ＝８．７Hｚ），７．１７（１H，ｄ，Ｊ＝１．８Hｚ），６．９７（１H，ｄ，Ｊ＝１．８Hｚ），６．８３（１H，ｄｄ，Ｊ＝１．８，８．７Hｚ），６．８０（１H，ｄｄ，Ｊ＝１．８，８．７Hｚ），６．６７（２H，ｄ，Ｊ＝８．１Hｚ），５．９６（１H，ｄ，Ｊ＝８．１Hｚ），５．８７（１H，ｔ，Ｊ＝４．８Hｚ），５．８５（１H，ｔ，Ｊ＝３．９Hｚ），５．３２（１H，ｄ，Ｊ＝４．５Hｚ），５．１０（１H，ｄ，Ｊ＝５．１Hｚ），４．９１（１H，ｄ，Ｊ＝４．８Hｚ），４．１２（２H，ｍ），４．０３（１H，ｍ），３．９１（２H，ｓ），３．７８（１H，ｍ），３．５０（２H，ｍ）

実施例５

構造式

【００４４】

【化１６】



で表される化合物。化合物Ａ３０ｍｇと３，５－ジヒドロキシメチルベンズアルデヒド２０ｍｇをメタノール６ｍｌに溶解し、酢酸２０ｍｌを加え、８０℃で３時間撹拌した。反応液を室温に戻し、シアノ水素化ほう素ナトリウム１０mg、１０％塩酸メタノール溶液数滴を加え、室温で３０分間撹拌した。反応液をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物２２ｍｇを得た。

Ｒｆ値：０．３５（メルク社製，キーゼルゲル６０F$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

FAB－MS（m／z）：６８４（M+）

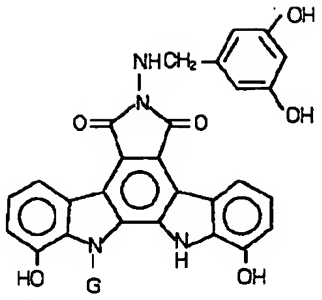
^{1}H－NMR（３００MHz，DMSO－d_6，δｐｐｍ）：１１．１９（１H，ｓ），９．７９（１H，ｓ），９．７６（１H，ｓ），８．８８（１H，ｄ，Ｊ＝８．７Hｚ），８．８０（１H，ｄ，Ｊ＝８．７Hｚ），７．３２（２H，ｓ），７．１８（２H，ｓ），６．９８（１H，ｄ，Ｊ＝１．８Hｚ），６．８１（２H，ｄｔ，Ｊ＝１．８，８．７Hｚ），５．９７（１H，ｄ，Ｊ＝８．７Hｚ），５．９３（１H，ｔ，Ｊ＝４．８Hｚ），５．８７（１H，ｔ，Ｊ＝３．２Hｚ），５．３４（１H，ｄ，Ｊ＝４．２Hｚ），５．１５（２H，ｔ，Ｊ＝６．３Hｚ），５．１２（１H，ｄ，Ｊ＝４．８Hｚ），４．９２（１H，ｄ，Ｊ＝４．８Hｚ），４．４９（２H，ｓ，），４．４７（２H，ｓ），４．２２（２H，ｄ，Ｊ＝５．１Hｚ），４．０３（１H，ｍ），３．９２（２H，ｓ），３．７８（１H，ｍ），３．５０（２H，ｍ）

実施例６

構造式

【００４５】

【化１７】



で表される化合物。化合物Ｂ５３ｍｇと３，５－ジヒドロキシベンズアルデヒド６９ｍｇをＮ，Ｎ－ジメチルホルムアミド３ｍｌに溶解し、８０℃で一晩撹拌した。反応液を減圧濃縮後、メタノール１０ｍｌに溶解し、過剰量のシアノ水素化ほう素ナトリウム、１０％塩酸メタノール溶液０．５ｍｌを加え、室温で３０分間撹拌した。反応液を減圧濃縮後、水を加え、酢酸エチル／メチルエチルケトン混合溶媒で抽出し、有機層を、飽和食塩水で洗浄後、乾燥濃縮した。残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物４．８ｍｇを得た。

Ｒｆ値：０．２（メルク社製，キーゼルゲル６０F_{254}，展開溶媒；クロロホルム：メタノール＝３：１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６５７$(M+H)^+$

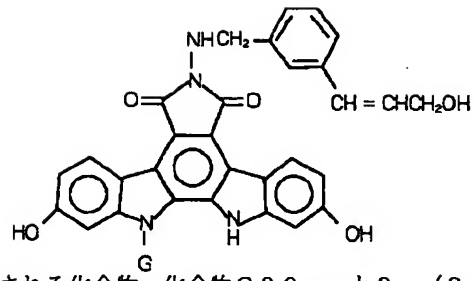
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１０．８９（１Ｈ，ｓ），１０．３３（１Ｈ，ｂｒ），９．９７（１Ｈ，ｂｒ），９．１１（１Ｈ，ｓ），８．７０（１Ｈ，ｄ，Ｊ＝６．８Ｈｚ），８．５２（１Ｈ，ｄ，Ｊ＝７．７Ｈｚ），７．１５～７．２１（２Ｈ，ｍ），６．９８～７．０６（３Ｈ，ｍ），６．３６（２Ｈ，ｄ，Ｊ＝１．９Ｈｚ），６．０６（１Ｈ，ｓ），５．９１（１Ｈ，ｔ，Ｊ＝５．４Ｈｚ），５．４１（１Ｈ，ｄ，Ｊ＝５．６Ｈｚ），５．３０～５．４５（１Ｈ，ｍ），５．２０（１Ｈ，ｄ，Ｊ＝４．６Ｈｚ），４．８７（１Ｈ，ｍ），３．９４～４．１０（４Ｈ，ｍ），３．５６～３．７７（３Ｈ，ｍ），３．３８～３．４３（２Ｈ，ｍ）

実施例７

構造式

【００４６】

【化１８】



で表される化合物。化合物Ｃ３０ｍｇと３－（３－ヒドロキシプロペニル）ベンジルヒドラジン　トリフルオロ酢酸塩　３０ｍｇをＮ，Ｎ－ジメチルホルムアミド２ｍｌに溶解し、トリエチルアミン数滴を加え、８０℃で一晩撹拌した。反応液を濃縮乾固後、残渣を分取薄層クロマトグラフィー（展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）により、精製した。表題の式で表される化合物８．２ｍｇを得た。

Ｒｆ値：０．５１（メルク社製，キーゼルゲル６０F_{254}，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：

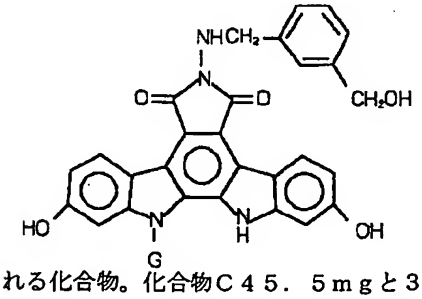
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１８（１Ｈ，ｓ），９．５０～１０．００（２Ｈ，ｂｒ），８．８６（１Ｈ，ｄ，Ｊ＝８．１Ｈｚ），８．７８（１Ｈ，ｄ，Ｊ＝８．５Ｈｚ），７．５９（１Ｈ，ｓ），７．２０～７．４０（３Ｈ，ｍ，），７．１６（１Ｈ，ｓ），６．９７（１Ｈ，ｓ），６．７３～６．８９（２Ｈ，ｍ），６．４２（１Ｈ，ｄ，Ｊ＝３．６Ｈｚ），６．３１～６．４８（１Ｈ，ｍ），６．１０（１Ｈ，ｔ，Ｊ＝４．０Ｈｚ），５．９５（１Ｈ，ｄ，Ｊ＝７．９Ｈｚ），５．８８（１Ｈ，ｂｒ，），５．３６（１Ｈ，ｂｒ），５．１３（１Ｈ，ｂｒ），４．９１（１Ｈ，ｂｒ），４．８４（１Ｈ，ｂｒ），４．２６（２Ｈ，ｓ），４．０９（２Ｈ，ｓ），３．７０～４．１０（４Ｈ，ｍ），３．４１～３．５８（２Ｈ，ｍ）

実施例８

構造式

【００４７】

【化１９】



で表される化合物。化合物Ｃ４５．５ｍｇと３－ヒドロ

キシメチルベンジルヒドラジン　トリフルオロ酢酸塩６７．２ｍｇをＮ，Ｎ－ジメチルホルムアミド３ｍｌに溶解し、飽和炭酸水素ナトリウム水溶液　数滴を加えて、７０℃で一晩撹拌した。反応液をメチルエチルケトンに希釈し、希塩酸、水、飽和食塩水で洗浄後、乾燥濃縮した。残渣を分取薄層クロマトグラフィー（展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）で粗精製後、セファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物１．６ｍｇを得た。

Ｒｆ値：０．４０（メルク社製，キーゼルゲル６０Ｆ$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６５４（M^+）

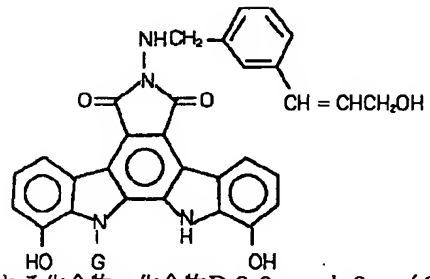
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１８（１Ｈ，ｓ），８．８６（１Ｈ，ｄ，Ｊ＝８．４Ｈｚ），８．７８（１Ｈ，ｄ，Ｊ＝８．７Ｈｚ），７．４２（１Ｈ，ｓ），７．４０（１Ｈ，ｄ，Ｊ＝７．５Ｈｚ），７．２７（１Ｈ，ｔ，Ｊ＝７．２Ｈｚ），７．１８（１Ｈ，ｄ，Ｊ＝７．５Ｈｚ），７．１７（１Ｈ，ｓ），６．９８（１Ｈ，ｄ，Ｊ＝１．８Ｈｚ），６．８１（２Ｈ，ｄｔ，Ｊ＝１．８，８．１Ｈｚ），６．００（１Ｈ，ｄｔ，Ｊ＝１．５，４．８Ｈｚ），５．９５（１Ｈ，ｄ，Ｊ＝８．７Ｈｚ），５．４３（１Ｈ，ｂｒ），５．１６（２Ｈ，ｂｒ），４．９３（１Ｈ，ｂｒ），４．４７（２Ｈ，ｓ），４．２５（１Ｈ，ｄ，Ｊ＝４．８Ｈｚ），４．１０（１Ｈ，ｂｒ），４．０２（１Ｈ，ｄ，Ｊ＝１０．８Ｈｚ），３．９０（２Ｈ，ｍ），３．７６（１Ｈ，ｍ）

実施例９

構造式

【００４８】

【化２０】



で表される化合物。化合物Ｄ３０ｍｇと３－（３－ヒドロキシプロペニル）ベンジルヒドラジン　トリフルオロ酢酸塩４０ｍｇをＮ，Ｎ－ジメチルホルムアミド１ｍｌに溶解し、トリエチルアミン　０．５ｍｌを加えて、８０℃で１．５時間撹拌した。反応液を酢酸エチル／メチルエチルケトン混合溶媒に希釈し、希塩酸、飽和食塩水で洗浄後、乾燥濃縮した。残渣を、セファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮、再びセファデックスＬＨ－２０のクロマト塔にかけエタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物７．８ｍｇを得た。

Ｒｆ値：０．４８（メルク社製，キーゼルゲル６０Ｆ$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

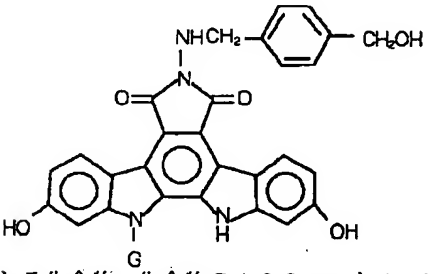
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１０．８９（１Ｈ，ｓ），１０．３５（１Ｈ，ｂｒ），９．９５（１Ｈ，ｂｒ），８．７０（１Ｈ，ｄ，Ｊ＝７．８Ｈｚ），８．５２（１Ｈ，ｄ，Ｊ＝７．８Ｈｚ），７．６０（１Ｈ，ｓ），６．９１～７．４０（８Ｈ，ｍ），６．５３（１Ｈ，ｄ，Ｊ＝１６．２Ｈｚ），６．３９（１Ｈ，ｔｄ，Ｊ＝４．６，１６．２Ｈｚ），６．１６（１Ｈ，ｔ，Ｊ＝５．６Ｈｚ），５．４１（１Ｈ，ｄ，Ｊ＝５．６Ｈｚ），５．３５（１Ｈ，ｂｒ），５．２０（１Ｈ，ｄ，Ｊ＝４．９Ｈｚ），４．８６（１Ｈ，ｔ，Ｊ＝３．６Ｈｚ），４．８４（１Ｈ，ｔ，Ｊ＝５．６Ｈｚ），４．２８（２Ｈ，ｓ），３．８９～４．１２（４Ｈ，ｍ），３．３０～３．７８（４Ｈ，ｍ）

実施例１０

構造式

【００４９】

【化２１】



で表される化合物。化合物Ｃ１００ｍｇと４－ヒドロキシメチルベンジルヒドラジン塩酸塩　１００ｍｇをＮ，Ｎ－ジメチルホルムアミド５ｍｌに溶解し、飽和炭酸水素ナトリウム水溶液　０．５ｍｌを加えて、室温で１時間、８０℃で３０分間、撹拌した。反応液をメチルエチルケトンに希釈し、２Ｎ塩酸、飽和食塩水で洗浄後、乾燥濃縮した。残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物３３ｍｇを得た。

Ｒｆ値：０．４７（メルク社製，キーゼルゲル６０Ｆ$_{254}$，展開溶媒；クロロホルム：メタノール：テトラヒドロフラン＝２：１：１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６５５（$M+H)^+$

^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１０（１Ｈ，ｂｒ），８．８３（１Ｈ，

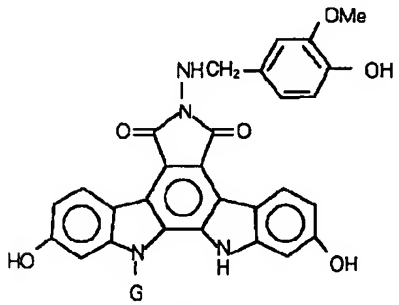
d，J＝9．3Hz），8．73（1H，d，J＝8．4Hz），7．44（2H，d，J＝8．4Hz），7．23（2H，d，J＝7．8Hz），7．11（1H，s），6．94（1H，s），6．78（2H，dt，J＝9．0，2．1Hz），6．02（1H，t，J＝4．8Hz），5．92（1H，d，J＝8．1Hz），4．80～5．23（2H，br），4．43（2H，s），4．24（2H，s），4．03（1H，m），3．90（2H，m），3．77（1H，m），3．50（2H，m），3．25～3．42（3H，m）

実施例１１

構造式

【００５０】

【化２２】



で表される化合物。化合物Ｃ５２ｍｇと３－メトキシ－４－ヒドロキシベンジルヒドラジン塩酸塩６１．４ｍｇをN，Ｎ－ジメチルホルムアミド２ｍｌに溶解し、飽和炭酸水素ナトリウム水溶液　０．５ｍｌを加えて、８０℃で１時間、撹拌した。反応液を、濃縮乾固した後、残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物２０ｍｇを得た。

Ｒｆ値：０．３３（メルク社製，キーゼルゲル６０F_{254}，展開溶媒；クロロホルム：メタノール：テトラヒドロフラン＝３：１：１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：$(M+H)^+$

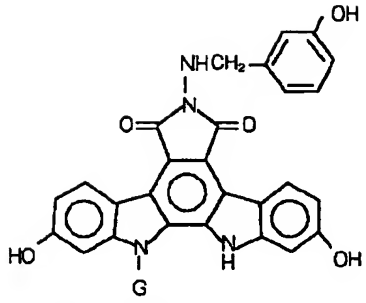
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１２（１Ｈ，ｓ），９．７７（１Ｈ，ｓ），９．７４（１Ｈ，ｓ），８．８６（１Ｈ，ｓ），８．７８（１Ｈ，ｄ，Ｊ＝８．６Ｈｚ），８．７６（１Ｈ，ｓ），７．１６（２Ｈ，ｄ，Ｊ＝８．１Ｈｚ），６．９７（１Ｈ，ｓ），６．７０～６．８５（３Ｈ，ｍ），６．６４（１Ｈ，ｄ，Ｊ＝８．５Ｈｚ），５．８６～６．０４（２Ｈ，ｍ），５．８５（１Ｈ，ｔ，Ｊ＝３．６Ｈｚ），５．３２（１Ｈ，ｄ，Ｊ＝３．９Ｈｚ），５．１０（１Ｈ，ｄ，Ｊ＝４．２Ｈｚ），４．９０（１Ｈ，ｄ，Ｊ＝４．３Ｈｚ），４．１１～４．２１（２Ｈ，ｍ），３．８６～４．１０（４Ｈ，ｍ），３．７７（３Ｈ，ｍ），３．３５～３．５２（２Ｈ，ｍ）

実施例１２

構造式

【００５１】

【化２３】



で表される化合物。化合物Ｃ４０ｍｇと３－ヒドロキシベンジルヒドラジン　塩酸塩　３１ｍｇをN，Ｎ－ジメチルホルムアミド２ｍｌに溶解し、飽和炭酸水素ナトリウム水溶液０．５ｍｌを加えて、８０℃で一晩、撹拌した。反応液を酢酸エチルに希釈し、２Ｎ塩酸、飽和炭酸水素ナトリウム水溶液、飽和食塩水で洗浄後、乾燥濃縮した。残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物１７．２ｍｇを得た。

Ｒｆ値：０．２４（メルク社製，キーゼルゲル６０F_{254}，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６４１ $(M+H)^+$

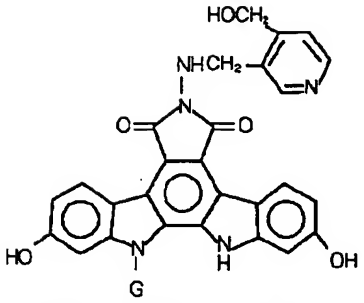
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１８（１Ｈ，ｓ），９．７６（１Ｈ，ｓ），９．７３（１Ｈ，ｓ），９．２８（１Ｈ，ｓ），８．８７（１Ｈ，ｄ，Ｊ＝８．５Ｈｚ），８．７９（１Ｈ，ｄ，Ｊ＝９．０Ｈｚ），７．１７（１Ｈ，ｓ），７．１８（１Ｈ，ｄｄ，Ｊ＝７．５，８．０Ｈｚ），６．９７（１Ｈ，ｄ，Ｊ＝２．３Ｈｚ），６．７８～６．９３（４Ｈ，ｍ），６．６０（１Ｈ，ｄｄ，Ｊ＝１．５，８．０Ｈｚ），５．９６（２Ｈ，ｍ），５．８５（１Ｈ，ｍ），５．３０（１Ｈ，ｄ，Ｊ＝４．２Ｈｚ），５．０９（１Ｈ，ｄ，Ｊ＝４．９Ｈｚ），４．９０（１Ｈ，ｄ，Ｊ＝５．１Ｈｚ），４．１５（２Ｈ，ｓ），３．７２～４．０５（４Ｈ，ｍ），３．５０（２Ｈ，ｍ）

実施例１３

構造式

【００５２】

【化２４】



で表される化合物。化合物Ａ４３ｍｇと（３－ｔ－ブチルジメチルシリルオキシメチル）－３－ピリジンカルバルデヒド１００ｍｇをメタノール１０ｍｌに懸濁し、酢酸１８ｍｌを加えて、８０℃で一晩撹拌した後に、反応液を濃縮しセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、残渣を、メタノール／テトラヒドロフラン（１：１）混合溶媒５ｍｌに溶解し、５％パラジウム炭素を加え、水素気流下室温で３．５時間撹拌した。反応溶液をセライト濾過し、残渣をテトラヒドロフラン５ｍｌに溶解し、過剰量のテトラブチルアンモニウムフルオリド（１．０Ｍテトラヒドロフラン溶液）を加え、室温で３０分間撹拌した。濃縮しセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物４．３ｍｇを得た。

Ｒｆ値：０．１（メルク社製，キーゼルゲル６０F_{254}，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６５６（Ｍ＋Ｈ）$^+$

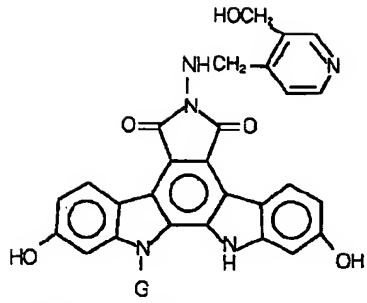
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１８（１Ｈ，ｓ），９．７５（１Ｈ，ｓ），９．７３（１Ｈ，ｓ），８．８４（１Ｈ，ｄ，Ｊ＝８．４Ｈｚ），８．７７（１Ｈ，ｄ，Ｊ＝８．９Ｈｚ），８．４２（１Ｈ，ｄ，Ｊ＝４．９Ｈｚ），８．３９（１Ｈ，ｓ），７．４８（１Ｈ，ｄ，Ｊ＝４．９Ｈｚ），７．１７（１Ｈ，ｄ，Ｊ＝１．１Ｈｚ），６．９７（１Ｈ，ｓ），６．７８～６．８３（２Ｈ，ｍ），６０９（１Ｈ，ｔ，Ｊ＝４．７Ｈｚ），５．９７（１Ｈ，ｄ，Ｊ＝６．６Ｈｚ），５．８４（１Ｈ，ｔ，Ｊ＝３．８Ｈｚ），５．３９（１Ｈ，ｔ，Ｊ＝５．８Ｈｚ），５．３０（１Ｈ，ｄ，Ｊ＝４．８Ｈｚ），５．０９（１Ｈ，ｄ，Ｊ＝４．２Ｈｚ），４．９５（２Ｈ，ｄ，Ｊ＝５．３Ｈｚ），４．９０（１Ｈ，ｄ，Ｊ＝３．３Ｈｚ），４．２７（２Ｈ，ｄ，Ｊ＝４．２Ｈｚ），３．７５～４．０３（４Ｈ，ｍ），３．４７～３．５２（２Ｈ，ｍ）

実施例１４

構造式

【００５３】

【化２５】



で表される化合物。化合物Ａ９８ｍｇと４－（３－ｔ－ブトキシメチル）ピリジンカルバルデヒド９２．１ｍｇをメタノール５ｍｌに溶解し、酢酸１８ｍｌを加え、８０℃で一晩撹拌した後に、反応液を濃縮し、得られた結晶をクロロホルムで洗浄した。これを、メタノール／テトラヒドロフラン（１：１）混合溶媒に溶解し、５％パラジウム炭素を加え水素気流下、３時間撹拌した。セライト濾過、濃縮後、残渣をテトラヒドロフランに溶解し、テトラブチルアンモニウムフルオリドを加え、室温で３０分間撹拌した。水を加え、メチルエチルケトンで抽出し、有機層を飽和食塩水で洗浄、濃縮した。セファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物１３．５ｍｇを得た。

Ｒｆ値：０．１０（メルク社製，キーゼルゲル６０F_{254}，展開溶媒；クロロホルム：メタノール：テトラヒドロフラン＝２：１：１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６５６（Ｍ＋Ｈ）$^+$

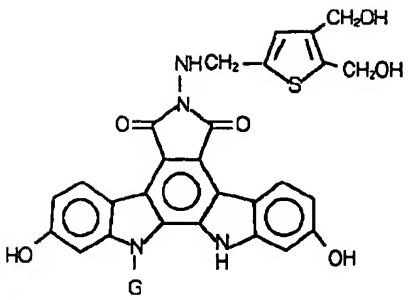
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１９（１Ｈ，ｓ），９．７８（１Ｈ，ｓ），９．７５（１Ｈ，ｓ）８．８５（１Ｈ，ｄ，Ｊ＝９．１Ｈｚ），８．７７（１Ｈ，ｄ，Ｊ＝９．１Ｈｚ），８．５１（１Ｈ，ｓ），８．１１（１Ｈ，ｄ，Ｊ＝５．１Ｈｚ），７．５９（１Ｈ，ｄ，Ｊ＝４．６Ｈｚ），７．１７（１Ｈ，ｄ，Ｊ＝２．１Ｈｚ），６．９７（１Ｈ，ｄ，Ｊ＝１．８Ｈｚ），６．７９～６．８５（２Ｈ，ｍ），６．２５（１Ｈ，ｔ，Ｊ＝５．０Ｈｚ），５．９８（１Ｈ，ｄ，Ｊ＝８．３Ｈｚ），５．８６（１Ｈ，ｄ，Ｊ＝４．５Ｈｚ），５．３２（１Ｈ，ｄ，Ｊ＝４．５Ｈｚ），５．２３（１Ｈ，ｔ，Ｊ＝５．６Ｈｚ），５．１１（１Ｈ，ｄ，Ｊ＝４．４Ｈｚ），４．９１（１Ｈ，ｄ，Ｊ＝４．９Ｈｚ），４．７４（２Ｈ，ｄ，Ｊ＝５．２Ｈｚ），４．３５（２Ｈ，ｄ，Ｊ＝７．８Ｈｚ），３．７３～４．０５（４Ｈ，ｍ），３．４３～３．５２（２Ｈ，ｍ）

実施例１５

構造式

【００５４】

【化２６】



で表される化合物。化合物Ａ５０ｍｇと（４、５－ｔ－ブチルジメチルシリルオキシメチル）チオフェン－２－カルボキシアルデヒド１００ｍｇを無水メタノール１０ｍｌに懸濁し、酢酸１００ｍｌを加えて、８０℃で２時間撹拌した。反応液をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、中間化合物４０ｍｇを得た。これをメタノール３ｍｌに懸濁し、シアノ水素化ほう素ナトリウム１２ｍｇ、１０％塩酸メタノール溶液３００ｍｌを加え、室温で１時間撹拌した。反応液を、セファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、分取薄層クロマトグラフィー（メルク社製、キーゼルゲル６０Ｆ２５４、展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）により、精製し、表題の式で表される化合物２６ｍｇを得た。

Ｒｆ値：０．２８（メルク社製，キーゼルゲル６０F_{254}，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６９０（M^+）

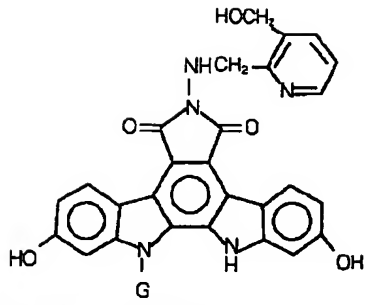
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１７（１Ｈ，ｓ），９．５０～１０．１５（２Ｈ，ｂｒ），８．８６（１Ｈ，ｄ，Ｊ＝８．４Ｈｚ），８．７８（１Ｈ，ｄ，Ｊ＝８．７Ｈｚ），７．１６（１Ｈ，ｄ，Ｊ＝１．８Ｈｚ），６．９７（１Ｈ，ｄ，Ｊ＝２．１Ｈｚ），６．９２（１Ｈ，ｓ），６．８２（１Ｈ，ｄｄ，Ｊ＝１．８，８．７Ｈｚ），６．７９（１Ｈ，ｄｄ，Ｊ＝２．１，８．４Ｈｚ），６．０４（１Ｈ，ｔ，Ｊ＝５．１Ｈｚ），６．０４（１Ｈ，ｔ．Ｊ＝５．１Ｈｚ），５．９６（１Ｈ，ｄ，Ｊ＝８．１Ｈｚ），５．８８（１Ｈ，ｂｒ），５．３５（１Ｈ，ｂｒ），５．２８（１Ｈ，ｂｒ），５．１５（１Ｈ，ｂｒ），４．９３（２Ｈ，ｂｒ），４．５３（２Ｈ，ｂｒ），４．７３（２Ｈ，ｄ，Ｊ＝４．５Ｈｚ），４．３０（１Ｈ，ｓ），４．００（１Ｈ，ｍ），３．９１（２Ｈ，ｍ），３．７７（１Ｈ，ｍ），３．５２（２Ｈ，ｍ）

実施例１６

構造式

【００５５】

【化２７】



で表される化合物。化合物Ａ３０ｍｇと２－（３－ｔ－ブチルジメチルシリルオキシメチル）ピリジルカルバルデヒド５０ｍｇをメタノール６ｍｌに懸濁し、酢酸３０ｍｍｌを加えて、８０℃で２時間撹拌した後に、セファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮し、中間化合物４０ｍｇを得た。これを、テトラヒドロフラン／メタノール（２：１）の混合溶媒に溶解し、シアノほう素化ナトリウム１５ｍｇ、塩酸メタノール溶液３ｍｌを加え、室温で３時間撹拌した。反応溶液を濃縮しセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物２７ｍｇを得た。

Ｒｆ値：０．１２（メルク社製，キーゼルゲル６０F_{254}，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６５６（Ｍ＋Ｈ）$^+$

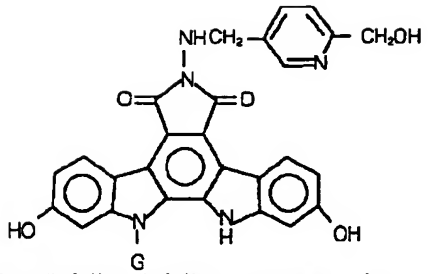
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１８（１Ｈ，ｂｒ），９，７７（２Ｈ，ｂｒ，）８，８２（１Ｈ，ｄ，Ｊ＝９．０Ｈｚ），８．７８４（１Ｈ，ｄ，Ｊ＝９．０Ｈｚ），８．２７（１Ｈ，ｄｄ，Ｊ＝１．８，５．１Ｈｚ），７．８３（１Ｈ，ｄ，Ｊ＝８．１Ｈｚ），７．２８（１Ｈ，ｄｄ，Ｊ＝８．１，５．１Ｈｚ），７．１７（１Ｈ，ｄ，Ｊ＝１．８Ｈｚ），６．９８（１Ｈ，ｄ，Ｊ＝１．８Ｈｚ），６．８２（１Ｈ，ｄｄ，Ｊ＝１．８，９．１Ｈｚ），６．７９（１Ｈ，ｄｄ，Ｊ＝１．８，９．０Ｈｚ），６．１５（１Ｈ，ｔ，Ｊ＝５．１Ｈｚ），５．９７（１Ｈ，ｄ，Ｊ＝８．１Ｈｚ），５．８６（１Ｈ，ｔ，Ｊ＝４．２Ｈｚ），５．３３（１Ｈ，ｄ，Ｊ＝５．４Ｈｚ），５．３１（１Ｈ，ｄ，Ｊ＝５．４Ｈｚ），５．１２（１Ｈ，ｄ，Ｊ＝４．８Ｈｚ），４．９３（１Ｈ，ｄ，Ｊ＝４．５Ｈｚ），４．８７（２Ｈ，ｄ，Ｊ＝６．０Ｈｚ），４．３６（２Ｈ，ｄ，Ｊ＝５．１Ｈｚ），４．０３（１Ｈ，ｍ），３．９１（２Ｈ，ｓ），３．７９（１Ｈ，ｍ），３．５１（２Ｈ，ｍ）

実施例１７

構造式

【００５６】

【化２８】



で表される化合物。化合物Ｃ３０ｍｇと（６－ヒドロキシメチル－３－ピリジルメチル）ヒドラジン塩酸塩６５ｍｇをＮ，Ｎ－ジメチルホルムアミド５ｍｌに溶解し、トリエチルアミン０．５ｍｌを加え、８０℃で３時間撹拌した後に、（６－ヒドロキシメチル－３－ピリジルメチル）ヒドラジン　塩酸塩３３ｍｇを加え、８０℃で２時間撹拌した。反応液を濃縮乾固後、セファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮し、残渣を再びセファデックスＬＨ－２０のクロマト塔にかけエタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物７．２ｍｇを得た。

ＦＡＢ－ＭＳ（ｍ／ｚ）：６５６（Ｍ＋Ｈ）$^{+}$

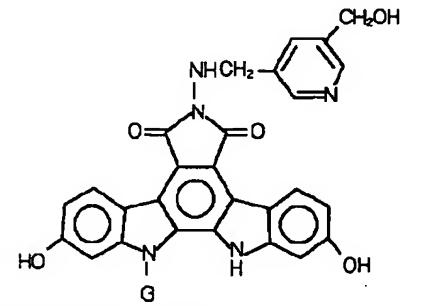
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１２（１Ｈ，ｂｒ），８．８１（１Ｈ，ｄ，Ｊ＝８．７Ｈｚ），８．７３（１Ｈ，ｄ，Ｊ＝８．７Ｈｚ），８．５１（１Ｈ，ｓ），７．９０（１Ｈ，ｄ，Ｊ＝７．９Ｈｚ），７．３９（１Ｈ，ｄ，Ｊ＝７．９Ｈｚ），７．１１（１Ｈ，ｓ），６．９３（１Ｈ，ｓ），６．７７（２Ｈ，ｔ，Ｊ＝８．７Ｈｚ），６．２１（１Ｈ，ｔ，Ｊ＝３．８Ｈｚ），５．９２（１Ｈ，ｄ，Ｊ＝７．９Ｈｚ），４．８５～５．５０（５Ｈ，ｂｒ），４．４８（２Ｈ，ｓ），４．２７（２Ｈ，ｄ，Ｊ＝３．８Ｈｚ），３．７０～４．０５（４Ｈ，ｍ），３．４５～３．５２（２Ｈ，ｍ）

実施例１８

構造式

【００５７】

【化２９】



で表される化合物。化合物Ｃ１２．５ｍｇと（５－ヒドロキシメチル－３－ピリジルメチル）ヒドラジン塩酸塩４２ｍｇをＮ，Ｎ－ジメチルホルムアミド１ｍｌに溶解し、トリエチルアミン０．１ｍｌを加えて、８０℃で２．５時間撹拌した後に、トリエチルアミン０．１ｍｌを加え、５０℃で一晩撹拌した。反応液を濃縮乾固後、セファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮し、残渣を再びセファデックスＬＨ－２０のクロマト塔にかけエタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物２．４ｍｇを得た。

Ｒｆ値：０．１８（メルク社製，キーゼルゲル６０Ｆ$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６５６（Ｍ＋Ｈ）$^{+}$

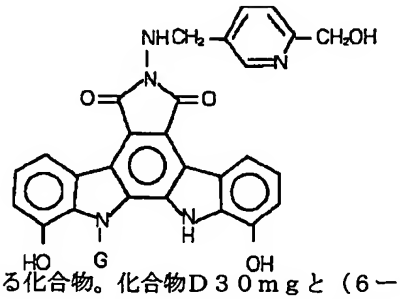
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１８（１Ｈ，ｂｒ），９．６０～１０．０２（２Ｈ，ｂｒ），８．８４（１Ｈ，ｄ，Ｊ＝８．５Ｈｚ），８．７６（１Ｈ，ｄ，Ｊ＝８．６Ｈｚ），８．５５（１Ｈ，ｓ），８．３７（１Ｈ，ｓ），７．８４（１Ｈ，ｓ），７．１６（１Ｈ，ｓ），７．００（１Ｈ，ｓ），６．７５～６．８５（２Ｈ，ｍ），６．２１（１Ｈ，ｔ，Ｊ＝４．７Ｈｚ），５．９５（１Ｈ，ｄ，Ｊ＝７．８Ｈｚ），５．８８～５．９５（１Ｈ，ｂｒ），５．４０～５．４８（１Ｈ，ｂｒ），５．２６～５．３５（１Ｈ，ｂｒ），５．１５～５．２５（１Ｈ，ｂｒ），４．９０～４．９３（１Ｈ，ｂｒ），４．５６（２Ｈ，ｄ，Ｊ＝４．７Ｈｚ），４．５０（２Ｈ，ｓ），３．７２～４．０５（４Ｈ，ｍ），３．４５～３．５５（２Ｈ，ｍ）

実施例１９

構造式

【００５８】

【化３０】



で表される化合物。化合物Ｄ３０ｍｇと（６－ヒドロキシメチル－３－ピリジルメチル）ヒドラジン塩酸塩６５ｍｇをＮ，Ｎ－ジメチルホルムアミド５ｍｌに溶解し、トリエチルアミン０．５ｍｌを加え、８０℃で１．５時間撹拌した。反応液を乾燥濃縮後、残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物２９ｍｇを得た。

ＦＡＢ－ＭＳ（ｍ／ｚ）：６５６（Ｍ＋Ｈ）$^{+}$

^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐ

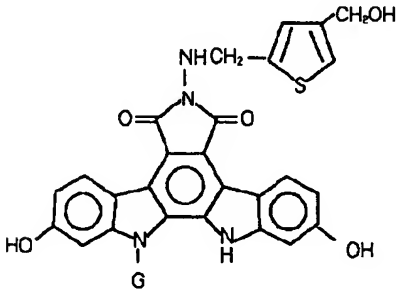
m）：10．89（1H，br），10．36（1H，br），9．97（1H，br），8．67（1H，d，J＝7．9Hz），8．52（1H，d，J＝2．2Hz），8．50（1H，d，J＝7．9Hz），7．93（1H，dd，J＝2．2，8．1Hz），7．41（1H，d，J＝8．1Hz），7．18（2H，t，J＝7．9Hz），7．02（1H，d，J＝7．9Hz），7．00（2H，t，J＝7．9Hz），6．29（1H，t，J＝4．5Hz），5．42（1H，d，J＝5．6Hz），5．33（1H，d，J＝6．1Hz），5．32（1H，t，J＝6．0Hz），5．21（1H，d，J＝5．3Hz），4．82～4．91（1H，br），4．48（2H，d，J＝6．0Hz），4．29（2H，d，J＝4．5Hz），3．91～4．12（2H，m），3．52～3．79（3H，m），3．30～3．40（1H，m）

実施例２０

構造式

【００５９】

【化３１】



で表される化合物。化合物Ｂ３０ｍｇと４－（ｔ－ブチルジメチルシリルオキシエチル）チオフェン－２－カルバルデヒド　１５２ｍｇを無水メタノール６ｍｌに懸濁し、酢酸　３０ｍｌを加えて、８０℃で２時間撹拌した。反応液をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出し、目的物を含む分画を濃縮乾固することにより、中間化合物３１ｍｇを得た。これをメタノール３ｍｌに懸濁し、シアノ水素化ほう素ナトリウム３０ｍｇ、１０％塩酸メタノール溶液３００ｍｌを加え、室温で１時間撹拌した。反応液を酢酸エチルで希釈し、水、飽和食塩水で洗浄し、乾燥濃縮した。残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物５ｍｇを得た。

Ｒｆ値：０．４３（メルク社製，トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６７５（Ｍ）$^{+}$

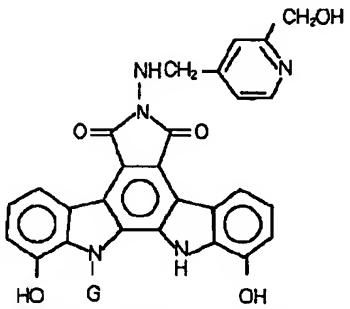
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１９（１Ｈ，ｓ），９．８０（２Ｈ，ｂｒ），８．８６（１Ｈ，ｄ，Ｊ＝９．０Ｈｚ），８．７８（１Ｈ，ｄ，Ｊ＝８．７Ｈｚ），７．１７（１Ｈ，ｄ，Ｊ＝１．８Ｈｚ），７．０３（１Ｈ，ｓ），６．９８（１Ｈ，ｄ，Ｊ＝２．１Ｈｚ），６．９５（１Ｈ，ｓ），６．８０（２Ｈ，ｄｔ，Ｊ＝２．１，８．７Ｈｚ），６．０８（１Ｈ，ｔ，Ｊ＝５．１Ｈｚ），５．９６（１Ｈ，ｄ，Ｊ＝７．８Ｈｚ），５．８９（１Ｈ，ｂｒ），５．３６（１Ｈ，ｂｒ），５．１３（１Ｈ，ｂｒ），４．９３（１Ｈ，ｂｒ），４．５７（１Ｈ，ｂｒ），４．３８（２Ｈ，ｄ，Ｊ＝４．２Ｈｚ），４．０５（２Ｈ，ｍ），３．９２（２Ｈ，ｓ），３．７７（１Ｈ，ｍ），３．５０（５Ｈ，ｍ）

実施例２１

構造式

【００６０】

【化３２】



で表される化合物。化合物Ｄ１７ｍｇと４－（２－ヒドロキシメチル－４－ピリジルメチル）ヒドラジン　トリフルオロ酢酸塩１２ｍｇをＮ，Ｎ－ジメチルホルムアミド２ｍｌに溶解し、トリエチルアミン０．１ｍｌを加えて、７５℃で２時間撹拌した。反応液に水、酢酸エチルを加え水で３回抽出した。水層に食塩を加え、メチルエチルケトンで３回抽出した。有機層を乾燥濃縮後、残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物８ｍｇを得た。

ＦＡＢ－ＭＳ（ｍ／ｚ）：６５６（Ｍ＋Ｈ）$^{+}$

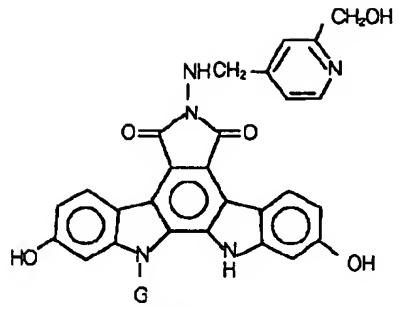
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１０．９０（１Ｈ，ｂｒ），８．６６（１Ｈ，ｄ，Ｊ＝７．６Ｈｚ），８．５０（１Ｈ，ｄ，Ｊ＝７．６Ｈｚ），８．４１（１Ｈ，ｄ，Ｊ＝５．０Ｈｚ），７．５７（１Ｈ，ｓ），７．４８（１Ｈ，ｄ，Ｊ＝５．０Ｈｚ），７．１７（２Ｈ，ｔ，Ｊ＝７．６Ｈｚ），７．０７（１Ｈ，ｄ，Ｊ＝７．６Ｈｚ），７．００（１Ｈ，ｄ，Ｊ＝７．６Ｈｚ），６．９８（１Ｈ，ｔ，Ｊ＝７．６Ｈｚ），６．３２（１Ｈ，ｔ，Ｊ＝４．８Ｈｚ），５．３６（１Ｈ，ｔ，Ｊ＝３．７Ｈｚ），５．１０～５．５０（４Ｈ，ｂｒ），４．５１（２Ｈ，ｄ，Ｊ＝３．７Ｈｚ），４．３４（２Ｈ，ｄ，Ｊ＝４．８Ｈｚ），３．９１～４．１２（２Ｈ，ｍ），３．５１～３．８０（３Ｈ，ｍ）

実施例２２

構造式

【００６１】

【化３３】



で表される化合物。化合物Ｃ１７ｍｇと（２－ヒドロキシメチル－４－ピリジルメチル）ヒドラジントリフルオロ酢酸塩１２ｍｇをＮ，Ｎ－ジメチルホルムアミド１ｍｌに溶解し、トリエチルアミン０．１ｍｌを加えて、８０℃で３．５時間撹拌した。反応液に水、酢酸エチルを加えて分液し、水層に食塩を加えメチルエチルケトンで抽出した。有機層を乾燥濃縮後、残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物４ｍｇを得た。

ＦＡＢ－ＭＳ（ｍ／ｚ）：６５６（Ｍ＋Ｈ$^{+}$）

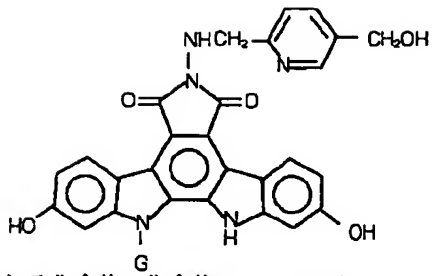
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１７（１Ｈ，ｂｒ），９．５５～１０．０５（２Ｈ，ｂｒ），８．８５（１Ｈ，ｄ，Ｊ＝８．４Ｈｚ），８．７７（１Ｈ，ｄ，Ｊ＝８．２Ｈｚ），８．４１（１Ｈ，ｄ，Ｊ＝５．１Ｈｚ），７．５６（１Ｈ，ｓ），７．４７（１Ｈ，ｄ，Ｊ＝５．１Ｈｚ），７．１５（１Ｈ，ｓ），６．９６（１Ｈ，ｓ），６．７２～６．８５（２Ｈ，ｍ），６．２６（１Ｈ，ｔ，Ｊ＝４．９Ｈｚ），５．９４（１Ｈ，ｄ，Ｊ＝８．６Ｈｚ），５．８０～５．９９（１Ｈ，ｂｒ），５．３０～５．４２（２Ｈ，ｂｒ），５．１０～５．２０（１Ｈ，ｂｒ），４．８５～４．９５（１Ｈ，ｂｒ），４．５１（２Ｈ，ｄ，Ｊ＝１．８Ｈｚ），４．３２（２Ｈ，ｄ，Ｊ＝４．５Ｈｚ），３．８９～４．０４（１Ｈ，ｍ），３．９０（２Ｈ，ｍ），３．７４～３．７８（１Ｈ，ｍ），３．５０（２Ｈ，ｍ）

実施例２３

構造式

【００６２】

【化３４】



で表される化合物。化合物Ａ１４ｍｇと５－ｔ－ブチルジメチルシリルオキシメチルピリジン－２－カルバルデヒド１４．７ｍｇを無水メタノール２ｍｌに懸濁し、酢酸８ｍｌを加えて、８０℃で一晩撹拌した。反応液セファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、中間化合物１５．３ｍｇを得た。シアノ水素化ほう素ナトリウム７５ｍｇをテトラヒドロフラン１ｍｌに懸濁し、塩化亜鉛（１．０Ｍジエチルエーテル溶液）０．５５ｍｌを滴下した。中間化合物１５．３ｍｇを、テトラヒドロフラン３ｍｌに懸濁して加え、室温で２．５時間撹拌した。反応液に飽和水炭酸水素ナトリウム水溶液を加え、メチルエチルケトンで抽出した。有機層を乾燥濃縮後、残渣をテトラヒドロフラン３ｍｌに溶解し、過剰量のテトラブチルアンモニウムフルオリド（１Ｍテトラヒドロフラン溶液）を０℃で滴下した。室温で３０分間撹拌後、水を加え、メチルエチルケトンで抽出した。有機層を乾燥濃縮後、残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物４．５ｍｇを得た。

Ｒｆ値：０．１（メルク社製，キーゼルゲル６０F_{254}，展開溶媒；クロロホルム：メタノール：テトラヒドロフラン＝３：１：１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６５６（Ｍ＋Ｈ）$^{+}$

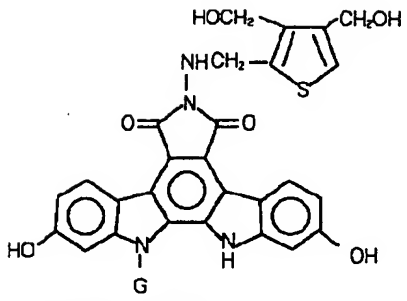
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１８（１Ｈ，ｓ），９．７７（２Ｈ，ｂｒ），８．８４（１Ｈ，ｄ，Ｊ＝８．５Ｈｚ），８．７６（１Ｈ，ｄ，Ｊ＝８．６Ｈｚ），８．３５（１Ｈ，ｄ，Ｊ＝１．７Ｈｚ），７．７２（２Ｈ，ｓ），７．１７（１Ｈ，ｄ，Ｊ＝１．７Ｈｚ），６．９８（１Ｈ，ｄ，Ｊ＝１．９Ｈｚ），６．７８～６．９８（２Ｈ，ｍ），６．２２（１Ｈ，ｔ，Ｊ＝４．６Ｈｚ），５．９６（１Ｈ，ｄ，Ｊ＝８．９Ｈｚ），５．８７（１Ｈ，ｂｒ），５．３５（１Ｈ，ｂｒ），５．２２（１Ｈ，ｔ，Ｊ＝２．０Ｈｚ），５．１１（１Ｈ，ｂｒ），４．９１（１Ｈ，ｂｒ），４．４６（２Ｈ，ｄ，Ｊ＝４．２Ｈｚ），４．３５（２Ｈ，ｄ，Ｊ＝４．６Ｈｚ），３．７３～４．０９（４Ｈ，ｍ），３．４９（２Ｈ，ｓ）

実施例２４

構造式

【００６３】

【化３５】



で表される化合物。化合物Ａ３０ｍｇと３，４－ビス－（ｔ－ブチルジメチルシリルオキシメチル）チオフェン－２－カルバルデヒド３０ｍｇを無水メタノール６ｍｌに懸濁し、酢酸３０ｍｌを加えて、８０℃で２時間撹拌した。反応液をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、中間化合物３１ｍｇを得た。これを、メタノール５ｍｌに懸濁し、シアノ水素化ほう素ナトリウム１０ｍｇ、１０％塩酸メタノール溶液１００ｍｌを加え、室温で３０分間撹拌した。反応液を酢酸エチルに希釈し、水、飽和食塩水で洗浄した。有機層を乾燥濃縮後、残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物２５ｍｇを得た。

Ｒｆ値：０．３０（メルク社製，キーゼルゲル６０Ｆ$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６９１（Ｍ＋Ｈ）$^{+}$

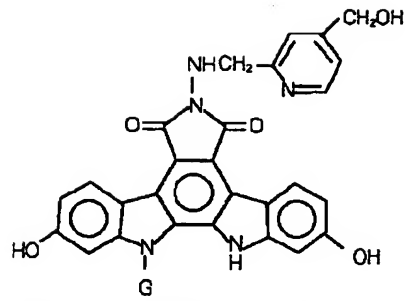
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－ｄ$_{6}$，δｐｐｍ）：１１．１９（１Ｈ，ｓ），９．７９（１Ｈ，ｓ），９．７６（１Ｈ，ｓ），８．８６（１Ｈ，ｄ，Ｊ＝８．４Ｈｚ），８．７８（１Ｈ，ｄ，Ｊ＝８．７Ｈｚ），７．１８（１Ｈ，ｄ，Ｊ＝１．８Ｈｚ），７．１５（１Ｈ，ｓ），６．９８（１Ｈ，ｄ，Ｊ＝２．１Ｈｚ），６．８２（２Ｈ，ｄｔ，Ｊ＝８．７，１．８Ｈｚ），６．０４（１Ｈ，ｔ，Ｊ＝５．４Ｈｚ），５．９７（１Ｈ，ｄ，Ｊ＝８．１Ｈｚ），５．８６（１Ｈ，ｔ，Ｊ＝３．６Ｈｚ），５．３３（１Ｈ，ｄ，Ｊ＝４．２Ｈｚ），５．１２（１Ｈ，ｄ，Ｊ＝４．２Ｈｚ），５．０１（１Ｈ，ｔ，Ｊ＝６．０Ｈｚ），４．９３（１Ｈ，ｄ，Ｊ＝４．８Ｈｚ），４．８５（１Ｈ，ｔ，Ｊ＝５．７Ｈｚ），４．５２（２Ｈ，ｄ，Ｊ＝５．７Ｈｚ），４．７０（２Ｈ，ｄ，Ｊ＝５．７Ｈｚ），４．４０（２Ｈ，ｄ，Ｊ＝４．８Ｈｚ），４．０１（１Ｈ，ｍ），３．９２（２Ｈ，ｍ），３．７７（１Ｈ，ｍ），３．５０（２Ｈ，ｍ）

実施例２５

構造式

【００６４】

【化３６】



で表される化合物。化合物Ａ１８ｍｇと４－ヒドロキシメチルピリジン－２－カルバルデヒド　７ｍｇを無水メタノール２ｍｌに懸濁し、酢酸　数滴を加えて、８０℃で１．５時間撹拌した。反応液を濃縮乾固後、セファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、中間化合物２２ｍｇを得た。シアノ水素化ほう素ナトリウム９０ｍｇをテトラヒドロフラン１ｍｌに懸濁し、塩化亜鉛（１．０Ｍジエチルエーテル溶液）０．６６ｍｌを滴下した。中間化合物２２ｍｇを、テトラヒドロフラン３ｍｌに懸濁して加え、室温で２．５時間撹拌した。反応液に水を加え、飽和炭酸水素ナトリウム水溶液で弱アルカリ性にし、酢酸エチルで抽出した。有機層を乾燥濃縮後、残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物１１ｍｇを得た。

ＦＡＢ－ＭＳ（ｍ／ｚ）：６５６（Ｍ＋Ｈ）$^{+}$

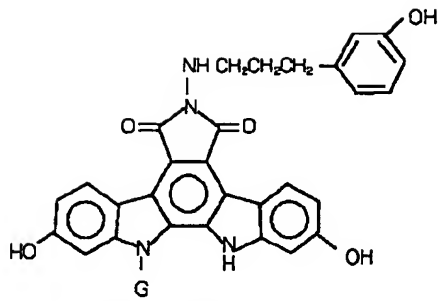
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－ｄ$_{6}$，δｐｐｍ）：１１．２１（１Ｈ，ｓ），９．８０（１Ｈ，ｓ），９．７７（１Ｈ，ｓ），８．８６（１Ｈ，ｄ，Ｊ＝８．６Ｈｚ），８．７８（１Ｈ，ｄ，Ｊ＝８．１Ｈｚ），７．８２～７．９５（１Ｈ，ｍ），７．６８～７．７５（１Ｈ，ｍ），７．３３～７．４３（１Ｈ，ｍ），７．１９（１Ｈ，ｓ），７．００（１Ｈ，ｓ），６．７８～６．８９（２Ｈ，ｍ），６．２２（１Ｈ，ｔ，Ｊ＝４．５Ｈｚ），５．９７（１Ｈ，ｄ，Ｊ＝７．９Ｈｚ），５．８６（１Ｈ，ｔ，Ｊ＝３．８Ｈｚ），５．３３（１Ｈ，ｄ，Ｊ＝４．２Ｈｚ），５．２９（１Ｈ，ｔ，Ｊ＝５．９Ｈｚ），５．１１（１Ｈ，ｄ，Ｊ＝５．０Ｈｚ），４．９１（１Ｈ，ｄ，Ｊ＝４．１Ｈｚ），４．４２（２Ｈ，ｄ，Ｊ＝５．５Ｈｚ），４．３３（２Ｈ，ｄ，Ｊ＝１．６Ｈｚ），３．９９～４．０９（１Ｈ，ｍ），３．９１（２Ｈ，ｍ），３．７２～３．８０（１Ｈ，ｍ），３．５０（２Ｈ，ｍ）

実施例２６

構造式

【００６５】

【化３７】



で表される化合物。化合物Ａ２０ｍｇと３－（３－ｔ－ブチルジメチルシリルオキシフェニル）プロパナール２０ｍｇを無水メタノール４ｍｌに懸濁し、酢酸２０ｍｌを加えて、８０℃で８時間撹拌した。反応液を濃縮し、セファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、中間化合物１４ｍｇを得た。これをメタノール５ｍｌに懸濁し、シアノ水素化ほう素ナトリウム７．５ｍｇ、１０％塩酸メタノール溶液０．５ｍｌを加え、室温で２時間撹拌した後、２Ｎ塩酸０．５ｍｌを加え、室温で一晩撹拌した。反応液を酢酸エチルで希釈し、水、飽和食塩水で洗浄した。有機層を乾燥濃縮後、残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物１２ｍｇを得た。

Ｒｆ値：０．３６（メルク社製，キーゼルゲル６０Ｆ$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６６９（Ｍ＋Ｈ）$^{+}$

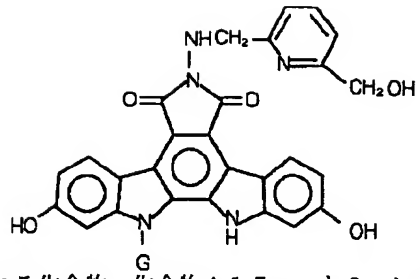
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－ｄ$_{6}$，δｐｐｍ）：１１．１８（１Ｈ，ｓ），９．６５（３Ｈ，ｂｒ），８．８７（１Ｈ，ｄ，Ｊ＝８．１Ｈｚ），８．７９（１Ｈ，ｄ，Ｊ＝８．１Ｈｚ），７．１７（１Ｈ，ｄ，Ｊ＝１．７Ｈｚ），７．０２（１Ｈ，ｔ，Ｊ＝８．１Ｈｚ），６．９８（１Ｈ，ｄ，Ｊ＝１．７Ｈｚ），６．８１（２Ｈ，ｄｔ，Ｊ＝１．７，５．７Ｈｚ），６．６４（１Ｈ，ｄ，Ｊ＝８．１Ｈｚ），６．６２（１Ｈ，ｓ），６．５７（１Ｈ，ｄｄ，Ｊ＝１．８，８．１Ｈｚ），５．９６（１Ｈ，ｄ，Ｊ＝８．１Ｈｚ），５．８７（１Ｈ，ｂｒ），５．７４（１Ｈ，ｔ，Ｊ＝４．８Ｈｚ），５．３５（１Ｈ，ｂｒ），５．１２（１Ｈ，ｂｒ），４．９２（１Ｈ，ｂｒ），４．０２（１Ｈ，ｄ，Ｊ＝１０．８Ｈｚ），３．９１（２Ｈ，ｍ），３．７９（１Ｈ，ｄ，Ｊ＝９．９Ｈｚ），３．５１（２Ｈ，ｄ，Ｊ＝７．５Ｈｚ），３．０２（２Ｈ，ｍ），２．６５（２Ｈ，ｔ，Ｊ＝７．２Ｈｚ），１．７２（２Ｈ，ｔ，Ｊ＝８．１Ｈｚ）

実施例２７

構造式

【００６６】

【化３８】



で表される化合物。化合物Ａ１５ｍｇと６－ヒドロキシメチルピリジン－２－カルバルデヒド６．９ｍｇを無水メタノール１ｍｌに懸濁し、酢酸を数滴加えて、８０℃で５時間撹拌した。反応液を濃縮乾固後、セファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、中間化合物５．２ｍｇを得た。シアノ水素化ほう素ナトリウム　６８ｍｇをテトラヒドロフラン２ｍｌに懸濁し、塩化亜鉛（１．０Ｍジエチルエーテル溶液）０．５ｍｌを滴下した。中間化合物５．２ｍｇを、テトラヒドロフラン１ｍｌに懸濁して加え、室温で一晩撹拌した。反応液に水を加え、飽和炭酸水素ナトリウム水溶液で弱アルカリ性にし、酢酸エチルで抽出した。有機層を乾燥濃縮後、残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物２．０ｍｇを得た。

Ｒｆ値：０．２９（メルク社製，キーゼルゲル６０Ｆ$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６５６（Ｍ＋Ｈ$^{+}$）

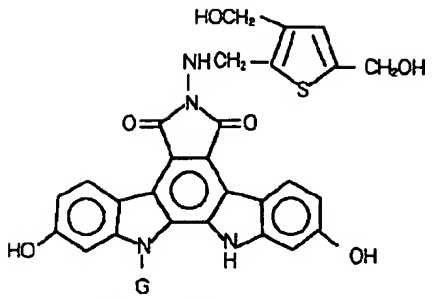
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－ｄ$_{6}$，δｐｐｍ）：１１．２１（１Ｈ，ｓ），９．８０（１Ｈ，ｓ），９．７７（１Ｈ，ｓ），８．８６（１Ｈ，ｄ，Ｊ＝８．６Ｈｚ），８．７８（１Ｈ，ｄ，Ｊ＝８．１Ｈｚ），７．８２～７．９５（１Ｈ，ｍ），７．６８～７．７５（１Ｈ，ｍ），７．３３～７．４３（１Ｈ，ｍ），７．１９（１Ｈ，ｓ），７．００（１Ｈ，ｓ），６．７８～６．８９（２Ｈ，ｍ），６．２２（１Ｈ，ｔ，Ｊ＝４．５Ｈｚ），５．９７（１Ｈ，ｄ，Ｊ＝７．９Ｈｚ），５．８６（１Ｈ，ｔ，Ｊ＝３．８Ｈｚ），５．３３（１Ｈ，ｄ，Ｊ＝４．２Ｈｚ），５．２９（１Ｈ，ｔ，Ｊ＝５．９Ｈｚ），５．１１（１Ｈ，ｄ，Ｊ＝５．０Ｈｚ），４．９１（１Ｈ，ｄ，Ｊ＝４．１Ｈｚ），４．４２（２Ｈ，ｄ，Ｊ＝５．５Ｈｚ），４．３３（２Ｈ，ｄ，Ｊ＝１．６Ｈｚ），３．９９～４．０９（１Ｈ，ｍ），３．９１（２Ｈ，ｍ），３．７２～３．８０（１Ｈ，ｍ），３．５０（２Ｈ，ｍ）

実施例２８

構造式

【００６７】

【化３９】



で表される化合物。化合物Ａ４０ｍｇと３，５－ビス－（ｔ－ブチルジメチルシリルオキシメチル）チオフェン－２－カルバルデヒド６０ｍｇを無水メタノール８ｍｌに懸濁し、酢酸　４０ｍｌを加えて、８０℃で２時間撹拌した。反応液をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、中間化合物　４６ｍｇを得た。これをメタノール５ｍｌに懸濁し、シアノ水素化ほう素ナトリウム３０ｍｇ、１０％塩酸メタノール溶液３００ｍｌを加え、室温で３０分間撹拌した。反応液を酢酸エチルで希釈し、水、飽和食塩水で洗浄した。有機層を乾燥濃縮後、残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物３６ｍｇを得た。

Ｒｆ値：０．２４（メルク社製，キーゼルゲル６０Ｆ$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６９０（Ｍ）$^{+}$

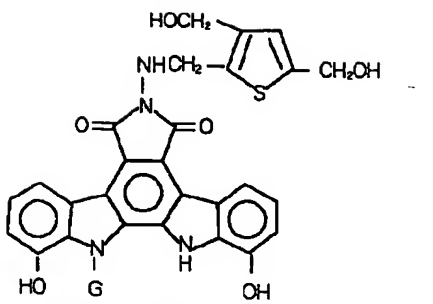
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－ｄ$_{6}$，δｐｐｍ）：１１．１９（１Ｈ，ｓ），９．７９（１Ｈ，ｓ），９．７６（１Ｈ，ｓ），８．８６（１Ｈ，ｄ，Ｊ＝８．４Ｈｚ），８．７８（１Ｈ，ｄ，Ｊ＝８．４Ｈｚ），７．１８（１Ｈ，ｄ，Ｊ＝１．８Ｈｚ），６．９８（１Ｈ，ｄ，Ｊ＝１．８Ｈｚ），６．８３（１Ｈ，ｓ），６．８２（２Ｈ，ｄｔ，Ｊ＝１．８，８．４Ｈｚ），５．９９（１Ｈ，ｔ，Ｊ＝４．８Ｈｚ），５．９７（１Ｈ，ｄ，Ｊ＝９．０Ｈｚ），５．８７（１Ｈ，ｔ，Ｊ＝４．２Ｈｚ），５．３５（１Ｈ，ｔ，Ｊ＝５．４Ｈｚ），５．３３（１Ｈ，ｄ，Ｊ＝４．８Ｈｚ），５．１２（１Ｈ，ｄ，Ｊ＝５．１Ｈｚ），４．９６（１Ｈ，ｄ，Ｊ＝５．７Ｈｚ），４．９４（１Ｈ，ｄ，Ｊ＝５．４Ｈｚ），４．４９（４Ｈ，ｔ，Ｊ＝６．６Ｈｚ），４．３４（２Ｈ，ｄ，Ｊ＝４．８Ｈｚ），４．０３（１Ｈ，ｍ），３．９２（２Ｈ，ｍ），３．７７（１Ｈ，ｍ），３．５０（２Ｈ，ｍ）

実施例２９

構造式

【００６８】

【化４０】



で表される化合物。化合物Ｂ５０ｍｇと３，５－ビス－（ｔ－ブチルジメチルシリルオキシメチル）チオフェン－２－カルバルデヒド６０ｍｇを無水メタノール／Ｎ，Ｎ－ジメチルホルムアミド（５：１）１２ｍｌに溶解し、酢酸５０ｍｌを加えて、８０℃で一晩撹拌した。反応液を酢酸エチルで希釈し、水、飽和食塩水で洗浄後、乾燥濃縮した。残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、残渣をテトラヒドロフラン／メタノール混合溶媒（２：１）６ｍｌに溶解し、シアノ水素化ほう素ナトリウム３０ｍｇ、１０％塩酸メタノール溶液３００ｍｌを加え、室温で１時間撹拌した。反応液を酢酸エチルで希釈し、飽和炭酸水素ナトリウム水溶液、飽和食塩水で洗浄した。有機層を乾燥濃縮後、残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物３７ｍｇを得た。

Ｒｆ値：０．３１（メルク社製，キーゼルゲル６０Ｆ$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６９０（Ｍ）$^{+}$

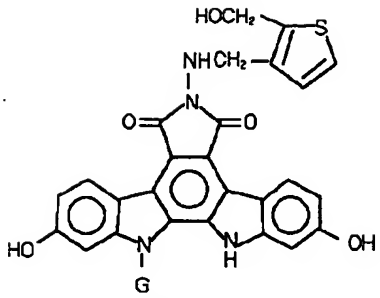
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－ｄ$_{6}$，δｐｐｍ）：１０．９０（１Ｈ，ｓ），１０．３７（１Ｈ，ｂｒ），９．９８（１Ｈ，ｂｒ），８．６９（１Ｈ，ｄ，Ｊ＝８．４Ｈｚ），８．５２（１Ｈ，ｄ，Ｊ＝８．４Ｈｚ），７．１９（２Ｈ，ｄｔ，Ｊ＝１．５，８．４Ｈｚ），７．０５（１Ｈ，ｄ，Ｊ＝８．６Ｈｚ），７．０１（２Ｈ，ｔ，Ｊ＝８．４Ｈｚ），６．８３（１Ｈ，ｓ），６．０４（１Ｈ，ｔ，Ｊ＝４．８Ｈｚ），５．４２（１Ｈ，ｄ，Ｊ＝５．７Ｈｚ），５．３５（２Ｈ，ｔ，Ｊ＝６．０Ｈｚ），５．２１（１Ｈ，ｄ，Ｊ＝５．４Ｈｚ），４．９５（１Ｈ，ｔ，Ｊ＝６．０Ｈｚ），４．９１（１Ｈ，ｂｒ），４．５０（４Ｈ，ｔ，Ｊ＝５．７Ｈｚ），４．３６（２Ｈ，ｄ，Ｊ＝５．４Ｈｚ），４．００（２Ｈ，ｍ），３．７３（１Ｈ，ｍ），３．６２（２Ｈ，ｍ），３．４０（１Ｈ，ｍ）

実施例３０

構造式

【００６９】

【化４１】



で表される化合物。化合物Ａ２０ｍｇと２－ヒドロキシメチルチオフェン－３－カルバルデヒド　２０ｍｇを無水メタノール４ｍｌに溶解し、酢酸２０ｍｌを加えて、８０℃で２時間撹拌した。反応液を減圧濃縮後、残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、残渣をテトラヒドロフラン／メタノール混合溶媒（２：１）３ｍｌに溶解し、シアノ水素化ほう素ナトリウム３０ｍｇ、１０％塩酸メタノール溶液３００ｍｌを加え、室温で３０分間撹拌した。反応液を減圧濃縮後、残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物１６ｍｇを得た。

Ｒｆ値：０．４９（メルク社製，キーゼルゲル６０Ｆ$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６６０（Ｍ）$^{+}$

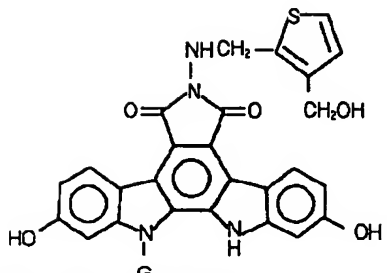
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－ｄ$_{6}$，δｐｐｍ）：１１．１８（１Ｈ，ｓ），９．７９（１Ｈ，ｓ），９．７５（１Ｈ，ｓ），８．８６（１Ｈ，ｄ，Ｊ＝８．４Ｈｚ），８．７８（１Ｈ，ｄ，Ｊ＝８．４Ｈｚ），７．３０（１Ｈ，ｄ，Ｊ＝４．８Ｈｚ），７．１７（１Ｈ，ｄ，Ｊ＝２．１Ｈｚ），７．０９（１Ｈ，ｄ，Ｊ＝５．４Ｈｚ），６．９８（１Ｈ，ｄ，Ｊ＝２．１Ｈｚ），６．８２（１Ｈ，ｄｄ，Ｊ＝２．１，８．４Ｈｚ），６．８０（１Ｈ，ｄｄ，Ｊ＝２．１，８．４Ｈｚ），５．９７（１Ｈ，ｄ，Ｊ＝８．１Ｈｚ），５．９２（１Ｈ，ｔ，Ｊ＝５．１Ｈｚ），５．８６（１Ｈ，ｔ，Ｊ＝３．９Ｈｚ），５．３７（１Ｈ，ｄ，Ｊ＝５．７Ｈｚ），５．３３（１Ｈ，ｄ，Ｊ＝４．５Ｈｚ），５．１２（１Ｈ，ｄ，Ｊ＝４．８Ｈｚ），４．９３（１Ｈ，ｄ，Ｊ＝４．８Ｈｚ），４．７６（２Ｈ，ｄ，Ｊ＝５．７Ｈｚ），４．２０（２Ｈ，ｄ，Ｊ＝５．１Ｈｚ），４．００（１Ｈ，ｍ），３．９１（２Ｈ，ｓ），３．７７（１Ｈ，ｍ），３．５０（２Ｈ，ｍ）

実施例３１

構造式

【００７０】

【化４２】



で表される化合物。化合物Ａ３０ｍｇと３－ｔ－ブチルジメチルシリルオキシメチルチオフェン－２－カルバルデヒド３０ｍｇを無水メタノール５ｍｌに溶解し、酢酸３０ｍｌを加えて、８０℃で２時間撹拌した。反応液を減圧濃縮後、残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、残渣をメタノール３ｍｌに懸濁し、シアノ水素化ほう素ナトリウム３０ｍｇ、１０％塩酸メタノール溶液３００ｍｌを加え、室温で１時間撹拌した。反応液をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物２４ｍｇを得た。

Ｒｆ値：０．４０（メルク社製、キーゼルゲル６０Ｆ２５４，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６６０（Ｍ）$^{+}$

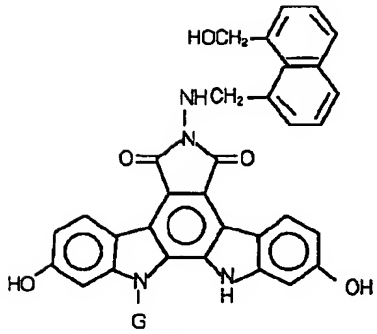
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－ｄ$_{6}$，δｐｐｍ）：１１．１９（１Ｈ，ｓ），９．７８（１Ｈ，ｓ），９．７５（１Ｈ，ｓ），８．８５（１Ｈ，ｄ，Ｊ＝８．７Ｈｚ），８．７８（１Ｈ，ｄ，Ｊ＝９．０Ｈｚ），７．３１（１Ｈｄ，Ｊ＝４．８Ｈｚ），７．１８（１Ｈ，ｄ，Ｊ＝１．８Ｈｚ），６．９９（１Ｈ，ｄ，Ｊ＝４．８Ｈｚ），６．９７（１Ｈ，ｄ，Ｊ＝１．８Ｈｚ），６．８１（２Ｈ，ｄｄＪ＝１．８，９．０Ｈｚ），６．０６（１Ｈ，ｔ，Ｊ＝４．８Ｈｚ），５．９７（１Ｈ，ｄ，Ｊ＝８．７Ｈｚ），５．８６（１Ｈ，ｔ，Ｊ＝３．９Ｈｚ），５．３３（１Ｈ，ｄ，Ｊ＝４．５Ｈｚ），５．１２（１Ｈ，ｄ，Ｊ＝４．５Ｈｚ），４．９９（１Ｈ，ｔ，Ｊ＝５．４Ｈｚ），４．９３（１Ｈ，ｄ，Ｊ＝５．１Ｈｚ），４．５３（２Ｈ，ｄ，Ｊ＝５．７Ｈｚ），４．３８（２Ｈ，ｄ，Ｊ＝４．８Ｈｚ），４．０２（１Ｈ，ｍ），３．９１（２Ｈ，ｍ），３．７７（１Ｈ，ｍ），３．５０（２Ｈ，ｍ）

実施例３２

構造式

【００７１】

【化４３】



で表される化合物。化合物Ａ３５ｍｇと８－ｔ－ブチルジメチルシリルオキシメチル－１－ナフトアルデヒド６０ｍｇをメタノール２ｍｌに懸濁し、酢酸を数滴加え、６０℃で２時間撹拌した。反応液を濃縮し、得られた固体をクロロフォルムで洗浄し、中間化合物　３２．５ｍｇを得た。シアノ水素化ほう素ナトリウム　６８ｍｇをテトラヒドロフラン３ｍｌに懸濁し、塩化亜鉛（１．０Ｍジエチルエーテル溶液）０．５ｍｌを滴下した。中間化合物３２．５ｍｇをテトラヒドロフラン２ｍｌに懸濁して加え、室温で２時間撹拌後、飽和食塩水を加え、酢酸エチル／メチルエチルケトンの混合溶媒で抽出した。有機層を乾燥濃縮し、残渣をテトラヒドロフラン１．５ｍｌに溶解し、テトラブチルアンモニウム　フロリド０．５ｍｌを加えた。室温で１．５時間撹拌後、酢酸エチル／メチルエチルケトンの混合溶媒で希釈し、水、飽和食塩水で洗浄し、有機層を乾燥濃縮し、セファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物３．３ｍｇを得た。

ＦＡＢ－ＭＳ（ｍ／ｚ）：７０５（Ｍ＋Ｈ）$^{+}$

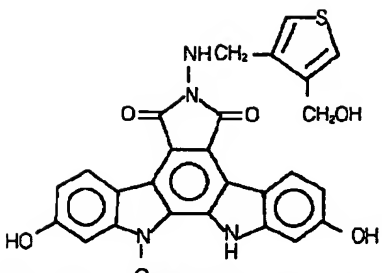
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１６（１Ｈ，ｓ），８．８４（１Ｈ，ｄ，Ｊ＝７．９Ｈｚ），８．７６（１Ｈ，ｄ，Ｊ＝７．９Ｈｚ），７．８７（２Ｈ，ｄ，Ｊ＝７．４Ｈｚ），７．６８（１Ｈ，ｄ，Ｊ＝７．４Ｈｚ），７．５８（１Ｈ，ｄ，Ｊ＝７．４Ｈｚ），７．４９（１Ｈ，ｄ，Ｊ＝７．４Ｈｚ），７．３９（１Ｈ，ｔ，Ｊ＝７．４Ｈｚ），７．１５（１Ｈ，ｓ），６．９７（１Ｈ，ｓ），６．８０（２Ｈ，ｔ．Ｊ＝７．９Ｈｚ），５．８６～６．００（３Ｈ，ｍ），５．４２（２Ｈ，ｓ），４．８５（２Ｈ，ｄ，Ｊ＝４．２Ｈｚ），４．８０～５．５０（４Ｈ，ｂｒ），３．７２～４．０５（４Ｈ，ｍ），３．４５～３．５９（２Ｈ，ｍ）

実施例３３

構造式

【００７２】

【化４４】



で表される化合物。化合物Ａ３０ｍｇと４－ｔ－ブチルジメチルシリルオキシチオフェン－３－カルバルデヒド３０ｍｇをメタノール６ｍｌに懸濁し、酢酸３０ｍｌを加え、８０℃で２時間撹拌した。反応液をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固し、これを、テトライドロフラン／メタノール混合溶媒（２：１）５ｍｌに溶解し、シアノ水素化ほう素ナトリウム　２０ｍｇ、１０％塩酸メタノール溶液２００ｍｌを加え、室温で３０分間撹拌した。反応液を酢酸エチルで希釈し、水、飽和食塩水で洗浄し、乾燥濃縮した。残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物１５ｍｇを得た。

Ｒｆ値：０．４７（メルク社製，キーゼルゲル６０Ｆ$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６６１（Ｍ＋Ｈ）$^{+}$

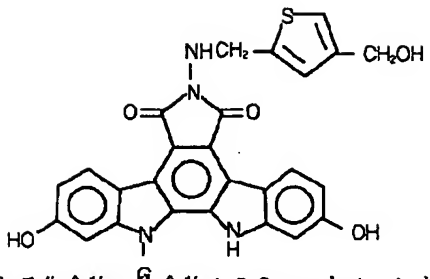
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１９（１Ｈ，ｓ），９．７９（１Ｈ，ｓ），９．７６（１Ｈ，ｓ），８．８６（１Ｈ，ｄ，Ｊ＝８．７Ｈｚ），８．７８（１Ｈ，ｄ，Ｊ＝８．７Ｈｚ），７．４３（１Ｈ，ｄ，Ｊ＝３．３Ｈｚ），７．３０（１Ｈ，ｄ，Ｊ＝３．６Ｈｚ），７．１７（１Ｈ，ｄ，Ｊ＝２．１Ｈｚ），６．９８（１Ｈ，ｄ，Ｊ＝２．１Ｈｚ），６．８３（１Ｈ，ｄｄ，Ｊ＝２．１，８．７Ｈｚ），６．８１（１Ｈ，ｄｄ，Ｊ＝２．１，８．７Ｈｚ），６．０４（１Ｈ，ｔ，Ｊ＝５．１Ｈｚ），５．９７（１Ｈ，ｄ，Ｊ＝９．０Ｈｚ），５．８７（１Ｈ，ｔ，Ｊ＝３．６Ｈｚ），５．３４（１Ｈ，ｄ，Ｊ＝３．９Ｈｚ），５．１２（１Ｈ，ｄ，Ｊ＝５．１Ｈｚ），５．１０（１Ｈ，ｔ，Ｊ＝５．１Ｈｚ），４．９２（１Ｈ，ｄ，Ｊ＝４．５Ｈｚ），４．６７（２Ｈ，ｄ，Ｊ＝５．４Ｈｚ），４．２３（２Ｈ，ｄ，Ｊ＝４．２Ｈｚ），４．０１（１Ｈ，ｍ），３．９２（２Ｈ，ｓ），３．７７（１Ｈ，ｍ），３．５０（２Ｈ，ｍ）

実施例３４

構造式

【００７３】

【化４５】



で表される化合物。化合物Ａ３８ｍｇと４－ヒドロキシメチルチオフェン－２－カルバルデヒド　２５ｍｇを無水メタノール７ｍｌに懸濁し、酢酸４５ｍｌを加えて、８０℃で７時間撹拌した。反応液を減圧濃縮後、メタノール／クロロホルムから結晶３８ｍｇを濾取した。この結晶をテトラヒドロフラン／メタノール（４：１）１０ｍｌに溶解し、シアノ水素化ほう素ナトリウム１３ｍｇ、１０％塩酸メタノール溶液０．５ｍｌを加え、室温で３０分間撹拌した。酢酸エチルに希釈し、飽和食塩水で洗浄後、乾燥濃縮した。残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物２１．７ｍｇを得た。

Ｒｆ値：０．２４（メルク社製、キーゼルゲル６０Ｆ$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

ＦＡＢ－ＭＳ（ｍ／ｚ）：６６０（Ｍ$^{+}$）

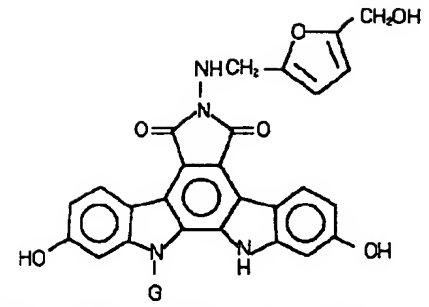
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－ｄ$_{6}$，δｐｐｍ）：１１．１９（１Ｈ，ｓ），９．７７（２Ｈ，ｂｒ），８．８６（１Ｈ，ｄ，Ｊ＝８．６Ｈｚ），８．７８（１Ｈ，ｄ，Ｊ＝８．６Ｈｚ），７．１７（１Ｈ，ｓ），７．１４（１Ｈ，ｄ，Ｊ＝１．８Ｈｚ），６．９８（２Ｈ，ｍ），６．８１（２Ｈ，ｄｔ，Ｊ＝１．８，６．９Ｈｚ），６．１２（１Ｈ，ｔ，Ｊ＝５．１Ｈｚ），５．９７（１Ｈ，ｄ，Ｊ＝８．１Ｈｚ），５．８７（１Ｈ，ｓ），５．３５（１Ｈ，ｄ，Ｊ＝１．８Ｈｚ），５．１３（１Ｈ，ｄ，Ｊ＝２．４Ｈｚ），５．０１（１Ｈ，ｔ，Ｊ＝５．４Ｈｚ），４．９３（１Ｈ，ｄ，Ｊ＝３．６Ｈｚ），４．４０（２Ｈ，ｄ，Ｊ＝４．５Ｈｚ），４．３４（２Ｈ，ｄ，Ｊ＝４．８Ｈｚ），４．００（１Ｈ，ｄｄ，Ｊ＝２．１，１１．６Ｈｚ），３．９１（２Ｈ，ｓ），３．７９（１Ｈ，ｍ），３．５１（２Ｈ，ｂｒ）

実施例３５

構造式

【００７４】

【化４６】



で表される化合物。化合物Ａ１０７ｍｇと５－ヒドロキシメチルフルフラール１２６ｍｇをメタノール２ｍｌに懸濁し、酢酸を数滴加え、８０℃で一晩撹拌した。反応液を濃縮し、得られた固体をクロロホルムで洗浄した。これを、メタノール／テトラヒドロフラン混合溶媒（１：２）５ｍｌに溶解し、シアノ水素化ほう素ナトリウム　６２．８ｍｇ、１０％塩酸メタノール溶液５ｍｌを加え、室温で３０分間撹拌した。反応液を酢酸エチル／メチルエチルケトンの混合溶媒で希釈し、水、飽和食塩水で洗浄した。有機層を乾燥濃縮し、セファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物１０３ｍｇを得た。

ＦＡＢ－ＭＳ（ｍ／ｚ）：６４４（Ｍ）$^{+}$

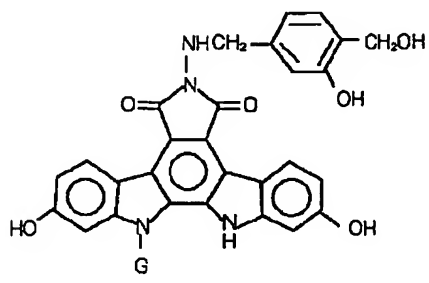
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－ｄ$_{6}$，δｐｐｍ）：１１．１９（１Ｈ，ｓ），９．７７（２Ｈ，ｂｒ），８．８５（１Ｈ，ｄ，Ｊ＝８．５Ｈｚ），８．７７（１Ｈ，ｄ，Ｊ＝８．６Ｈｚ），７．１８（１Ｈ，ｄ，Ｊ＝２．１Ｈｚ），６．９８（１Ｈ，ｄ，Ｊ＝１．７Ｈｚ），６．７５～６．８６（２Ｈ，ｍ），６．３１（１Ｈ，ｄ，Ｊ＝３．１Ｈｚ），６．１５（１Ｈ，ｄ，Ｊ＝３．１Ｈｚ），６．０３（１Ｈ，ｔ，Ｊ＝４．７Ｈｚ），５．９７（１Ｈ，ｄ，Ｊ＝８．３Ｈｚ），５．８７（１Ｈ，ｔ，Ｊ＝３．６Ｈｚ），５．３４（１Ｈ，ｄ，Ｊ＝３．９Ｈｚ），５．０８～５．１５（２Ｈ，ｍ），４．９３（１Ｈ，ｄ，Ｊ＝４．５Ｈｚ），４．２８（２Ｈ，ｄ，Ｊ＝５．６Ｈｚ），４．２０（２Ｈ，ｄ，Ｊ＝４．７Ｈｚ），３．７２～４．０５（４Ｈ，ｍ），３．４５～３．５５（２Ｈ，ｍ）

実施例３６

構造式

【００７５】

【化４７】



で表される化合物。化合物Ａ３９ｍｇと３－ヒドロキシ－４－ヒドロキシメチルベンズアルデヒド３３ｍｇをメタノール８ｍｌに懸濁し、酢酸１５０μｌを加え、室温で三晩撹拌した。反応液を濾過し、得られた固体をクロロホルムで洗浄した。これを、メタノール／テトラヒドロフラン混合溶媒（１：２）５ｍｌに溶解し、シアノ水素化ほう素ナトリウム　９ｍｇ、１０％塩酸メタノール溶液　数滴を加え、室温で１時間撹拌した。反応液を減圧乾固し、セファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物３．５ｍｇを得た。

ＦＡＢ－ＭＳ（ｍ／ｚ）：６７０（M^+）

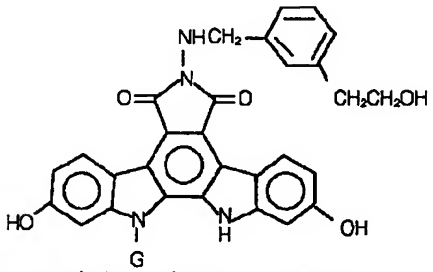
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１８（１Ｈ，ｓ），９．７７（１Ｈ，ｓ），９．７６（１Ｈ，ｓ），９．２８（１Ｈ，ｂｒ），８．８７（１Ｈ，ｄ，Ｊ＝８．５Ｈｚ），８．７８（１Ｈ，ｄ，Ｊ＝８．５Ｈｚ），７．１８（１Ｈ，ｄ，Ｊ＝７．９Ｈｚ），７．１７（１Ｈ，ｓ），６．９７（１Ｈ，ｄ，Ｊ＝２．０Ｈｚ），６．７７～６．９３（４Ｈ，ｍ），５．９６（１Ｈ，ｄ，Ｊ＝８．２Ｈｚ），５．９２（１Ｈ，ｔ，Ｊ＝５．０Ｈｚ），５．８６（１Ｈ，ｔ，Ｊ＝３．２Ｈｚ），５．３３（１Ｈ，ｄ，Ｊ＝４．３Ｈｚ），５．１２（１Ｈ，ｄ，Ｊ＝４．６Ｈｚ），４．９２（１Ｈ，ｄ，Ｊ＝５．０Ｈｚ），５．８３（１Ｈ，ｂｒ），４．４１（２Ｈ，ｄ，Ｊ＝３．２Ｈｚ），４．１４（２Ｈ，ｄ，Ｊ＝５．０Ｈｚ），４．００（１Ｈ，ｍ），３．９０（２Ｈ，ｍ），３．７８（１Ｈ，ｍ），３．５０（２Ｈ，ｍ）

実施例３７

構造式

【００７６】

【化４８】



で表される化合物。化合物Ａ３０ｍｇと３－（２－ヒドロキシエチル）ベンズアルデヒド２４．９ｍｇをメタノール１ｍｌに懸濁し、酢酸を数滴加え、８０℃で１時間撹拌した。反応液を減圧濃縮後、残渣をクロロホルムで洗浄した。これを、メタノール２ｍｌに懸濁し、シアノ水素化ほう素ナトリウム　９．０ｍｇ、１０％塩酸メタノール溶液　数滴を加え、室温で３０分間撹拌した。反応液を減圧乾固した残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物２０．７ｍｇを得た。

ＦＡＢ－ＭＳ（ｍ／ｚ）：６６９（Ｍ＋Ｈ）$^+$

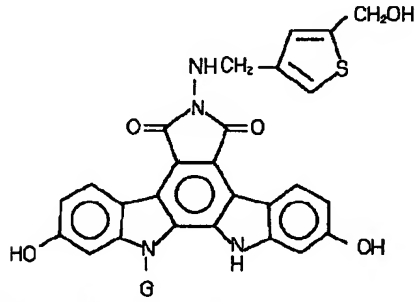
^{1}Ｈ－ＮＭＲ（３００ＭＨｚ，ＤＭＳＯ－d_6，δｐｐｍ）：１１．１８（１Ｈ，ｓ），９．７８（１Ｈ，ｓ），９．７５（１Ｈ，ｓ），８．８７（１Ｈ，ｄ，Ｊ＝８．５Ｈｚ），８．７９（１Ｈ，ｄ，Ｊ＝８．６Ｈｚ），７．３６（１Ｈ，ｓ），７．３２（１Ｈ，ｄ，Ｊ＝７．６Ｈｚ），７．１５～７．２５（２Ｈ，ｍ），７．０７（１Ｈ，ｄ，Ｊ＝７．６Ｈｚ），６．９７（１Ｈ，ｄ，Ｊ＝２．０Ｈｚ），６．７５～６．８５（２Ｈ，ｍ），６．０２（１Ｈ，ｄ，Ｊ＝５．２Ｈｚ），５．９６（１Ｈ，ｄ，Ｊ＝８．２Ｈｚ），５．８６（１Ｈ，ｔ，Ｊ＝３．３Ｈｚ），５．３３（１Ｈ，ｄ，Ｊ＝４．３Ｈｚ），５．１１（１Ｈ，ｄ，Ｊ＝４．９Ｈｚ），４．９０（１Ｈ，ｄ，Ｊ＝５．４Ｈｚ），４．６１（１Ｈ，ｔ，Ｊ＝５．３Ｈｚ），４．２３（２Ｈ，ｄ，Ｊ＝４．５Ｈｚ），３．７２～４．０５（４Ｈ，ｍ），３．４５～３．６０（４Ｈ，ｍ），２．６９（２Ｈ，ｔ，Ｊ＝７．３Ｈｚ）

実施例３８

構造式

【００７７】

【化４９】



で表される化合物。化合物Ａ４０ｍｇと５－ヒドロキシメチルチオフェン－３－カルバルデヒド　４０ｍｇをメタノール８ｍｌに懸濁し、酢酸４０ｍｌを加え、８０℃で３時間撹拌した。反応液を室温に冷却し、クロロホルムを加え、粉体を濾取した。これを、メタノール５ｍｌに懸濁し、シアノ水素化ほう素ナトリウム２０ｍｇ、１０％塩酸メタノール溶液２００ｍｌを加え、室温で３０分間撹拌した。反応液を酢酸エチル／メチルエチルケトンの混合溶媒で希釈し、水、飽和食塩水で洗浄し、乾燥濃縮した。残渣をセファデックスＬＨ－２０のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物２１ｍｇを得た。

Ｒｆ値：０．２９（メルク社製，キーゼルゲル６０Ｆ$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝４：２：２：０．５：０．１）

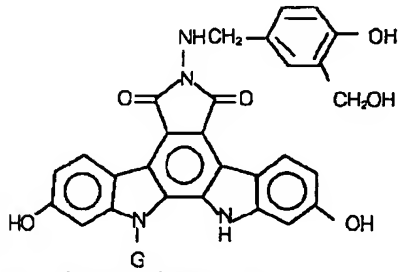
FAB－MS（m／z）：660（M^+）
^{1}H－NMR（300MHz，DMSO－d_6，δppm）：11.19（1H，s），9.80（2H，br），8.86（1H，d，J＝9.0Hz），8.79（1H，d，J＝8.7Hz），7.34（1H，s），7.17（1H，d，J＝1.5Hz），7.04（1H，s），6.97（1H，d，J＝1.5Hz），6.82（1H，dd，J＝1.5，9.0Hz），6.80（1H，dd，J＝8.7，1.5Hz），5.97（2H，t，J＝5.1Hz），5.87（1H，br），5.40（1H，t，J＝6.0Hz），5.35（1H，br），5.13（1H，s），4.91（1H，d，J＝3.9Hz），4.57（2H，d，J＝4.2Hz），4.20（2H，d，J＝4.8Hz），3.88～4.10（3H，m），3.78（1H，m），3.50（2H，m）

実施例39

構造式

【0078】

【化50】



で表される化合物。化合物A38mgと3－ヒドロキシメチル－4－ヒドロキシベンズアルデヒド91mgをN，Nージメチルホルムアミド2mlに溶解し、酢酸3滴を加え、80℃で3時間撹拌した。反応液を減圧濃縮後、残渣をクロロホルムで洗浄した。これを、メタノール3mlに懸濁し、シアノ水素化ほう素ナトリウム 40mg、10%塩酸メタノール溶液数滴を加え、室温で30分間撹拌した。反応液をセファデックスLH－20のクロマト塔にかけメタノールで溶出した。目的物を含む分画を濃縮乾固することにより、表題の式で表される化合物8．9mgを得た。

Rf値：0．15（メルク社製，キーゼルゲル60F$_{254}$，展開溶媒；アセトニトリル：テトラヒドロフラン：トルエン：水：酢酸＝4：2：2：0．5：0．1）

FAB－MS（m／z）：

^{1}H－NMR（300MHz，DMSO－d_6，δppm）：11.19（1H，s），9.75（1H，br），9.74（1H，br），9.23（1H，br），8.87（1H，d，J＝8.6Hz），8.79（1H，d，J＝8.6Hz），7.37（1H，s），7.12～7.20（2H，m），6.98（1H，d，J＝2.1Hz），6.75～6.85（2H，m），6.70（1H，d，J＝8.3Hz），5.97（1H，d，J＝8.3Hz），5.86（1H，t，J＝4.4Hz），5.76（1H，t，J＝5.3Hz），5.33（1H，d，J＝4.4Hz），5.10（1H，d，J＝3.4Hz），4.89～4.98（2H，m），4.44（2H，d，J＝4.5Hz），3.72～4.15（6H，m），3.48～3.55（2H，m）

【0079】

【発明の効果】本発明の化合物は、優れた抗腫瘍効果を有することから医薬の分野において抗腫瘍剤として有用である。

【0080】

フロントページの続き

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